



# ANNALS OF INTERNAL MEDICINE

---

VOLUME 29

JULY, 1948

NUMBER 1

---

## MODIFICATION OF FAT ABSORPTION IN THE DIGESTIVE TRACT BY THE USE OF AN EMULSIFYING AGENT\*

By CHESTER M. JONES, M.D., F.A.C.P., PERRY J. CULVER, M.D., GLADYS  
D. DRUMMEY, B.S. and ANNA E. RYAN, B.A., *Boston, Massachusetts*

NUTRITIONAL disorders of clinical importance are due to a variety of factors. Thus malnutrition may be secondary to an inadequate food intake due to loss of appetite or to organic disease interfering with the ingestion of food. It may be caused by an abnormal increase in the metabolic requirements of the body, as in Graves' disease or in febrile states. It may be associated with an inadequate utilization of food absorbed from the digestive tract, as in diabetes or chronic severe hepatic disorders. Undernutrition may also be the result of a diminution in the absorptive powers of the small bowel, secondary to an intrinsic physiological disturbance or to a reduction of the total area of absorbing surface of the jejunum or ileum. Finally, it is probable that faulty absorption of food substances occurs because of a grossly increased intestinal rate.

Among those disturbances interfering with proper food absorption, conditions such as sprue or celiac disease may serve as examples of a physiological abnormality involving the function of the small bowel. Reduction of the area of absorbing surface may be due to a chronic inflammatory process, such as regional enteritis, or to entero-anastomoses which short circuit large portions of the small intestine. Pancreatic fibrosis, with a striking diminution of the digestive enzymes, may cause impaired absorption of foodstuffs because of incomplete or delayed breakdown of proteins, fats and carbohydrates. In each of these conditions, the loss of calorific material is most marked as a result of the failure properly to absorb ingested fats. Steator-

\* Presented at the Twenty-ninth Session of the American College of Physicians, San Francisco, April 20, 1948.

From the Department of Medicine, Harvard University, and the Medical Service of the Massachusetts General Hospital, Boston. This work was made possible by the "Fund for Studies in Intestinal Absorption," a grant from the Atlas Powder Company, Wilmington, Delaware.



rhea is one of the striking clinical features to be noted in cases of sprue, pancreatic fibrosis, and following major anastomotic short circuits of the small intestine. Whereas normally the fat content of the stools comprises not more than 4 per cent of ingested fats,<sup>1</sup> under these conditions fecal lipid content may run as high as 40 to 50 per cent of the dietary intake.

Another, as yet unexplained, cause of undernutrition that is of great physiological interest is the operation, subtotal gastrectomy. We have found, as have other observers, that following this procedure an important number of patients remain poorly nourished in spite of an apparently adequate food intake. In this group, one commonly finds an excessive quantity of fat in the stools, which may contain as much as 40 to 45 per cent of ingested lipid material.<sup>2</sup>

In all of these conditions, nutritional improvement can be obtained with varying degrees of success. Thus in sprue, the use of liver extract or of folic acid in optimal amounts may result in increased intestinal absorption. In this disease, however, the results are variable, and it is rare in so-called nontropical sprue to modify the flat vitamin A tolerance curve so characteristic of this condition. In pancreatic fibrosis, potent pancreatic extracts occasionally may be of great clinical benefit. In patients with a major loss of absorptive surface, secondary to an inflammatory process or to short circuiting operations, overfeeding may be the only therapeutic measure to afford help. In our experience, this has also been true in the treatment of malnutrition secondary to subtotal gastrectomy. Strenuous and prolonged overfeeding imposes real difficulties on both patient and physician, and at times presents an almost insuperable problem.

Because of the underlying deficiencies in fat absorption inherent in the several conditions that have been mentioned, search has been made to determine if other measures can be found which might improve the uptake of fat from the bowel in diseases affecting the function of the small intestine. Certain substances have been developed commercially as emulsifying agents and have been used in industry to effect an even distribution of flavors, perfumes and lipid substances in an aqueous or lipid medium. These agents possess emulsifying and "wetting" properties due to their effect on surface tension. Dubos,<sup>3</sup> in 1945, reported the use of one of these agents known as "Tween 60" for the dispersion of tubercle bacilli in an aqueous culture medium. The effect of this substance on the lipid encapsulated tubercle bacilli was to produce a homogeneous dispersion of the organisms in the culture medium in such a manner that individual colonies could be grown in place of the usual growth in the form of a pellicle. These observations of Dubos suggested the possibility that the use of such an agent, when mixed with food, might provide a more homogeneous and finer emulsification of dietary fats and a better dispersal of lipid substances when presented to the intestinal mucosa for absorption. We chose the substance polyoxyethylene sorbitan monooleate \*

\* Sold under the registered Trade Mark "Tween 80" and supplied for this study through the courtesy of the Atlas Powder Company, Wilmington, Delaware.

(hereafter referred to as "PSM") for study of this problem. This preparation is the direct reaction product of sorbitan monooleate with ethylene oxide in the ratio of 20 mols of ethylene oxide per mol of sorbitan monooleate.

Long term feeding experiments by Krantz <sup>4</sup> have shown that no toxic manifestations have followed the feeding of PSM to animals over several generations. In human beings, we have fed as much as 15.0 grams daily for a period of months without any untoward symptoms and without any evidence of toxicity as measured by erythrocyte or white cell changes, liver or renal function tests. In collaboration with the Central Research Laboratory of the Atlas Powder Company we have demonstrated <sup>5</sup> that at least the polyoxyethylene fraction of PSM is excreted quantitatively in the urine and stools. The possibility of oxalic acid poisoning from the polyoxyethylene component would seem, therefore, to be negligible. Furthermore, urinary studies for oxalate content in patients on PSM therapy indicate no increase in oxaluria. The only symptom attributable to the use of this preparation has been the rare manifestation of increased bowel activity.

In order to study the effectiveness of any agent in modifying the absorption of fat from the intestinal tract in human beings, observations obviously may be directed along several lines.

In human subjects on a diet of fixed caloric and fixed fat content, measurements may be made of the daily fat loss in the stools under controlled experimental conditions. Improvements in fat absorption will be reflected in a reduction in fecal fat. Such studies are extremely time-consuming and are possible only on a metabolic ward where diets can be accurately measured and excreta carefully collected. Collection periods must be at least of six or seven days' duration in order to obtain adequate samples, and it is preferable that 12 to 14 day periods be used to obtain conclusive results. Careful and thorough mixing of stools is a difficult procedure but is essential for satisfactory results.

A second method of studying fat absorption, which may be used in an ambulatory patient, is that of following variations in weight over long periods of time, with relative stabilization of activity, dietary intake and therapeutic measures. Conclusions as to the efficacy of a given therapeutic measure under such conditions are of relative value only, but with an intelligent, coöperative patient, valuable studies of this nature may be carried out over intervals of many months.

A third approach to the problem is to attempt to evaluate fat absorption by the oral administration of a fat-soluble substance and the subsequent determination of blood levels of the given substance at regular time intervals. A so-called vitamin A tolerance curve is such a procedure.

We have employed all three measures in attempting to demonstrate the effectiveness of PSM in improving the absorption of fats in human beings.

The first set of observations is shown in figure 1 and represents a composite of vitamin A tolerance curves taken under standard conditions in a

group of 16 normal subjects. Serum vitamin A determinations were made by the method of May et al.<sup>6</sup> on specimens taken fasting and at intervals of three, five and seven hours after the ingestion of 200,000 units of vitamin A ester in fish liver oil. Two weeks after the original control studies were made the tests were repeated, but at this time 2.0 grams of PSM were added to the capsules containing the fatty solution of vitamin A. Figure 1 represents the composite curves obtained in the normal subjects before and after the addition of PSM to the vitamin A test dose. The peak level of vitamin A obtained in the serum is essentially the same in the control curves and following the use of an emulsifying agent. Such a result is probably to be expected, inasmuch as 96 per cent or more of ingested fat is absorbed by nor-

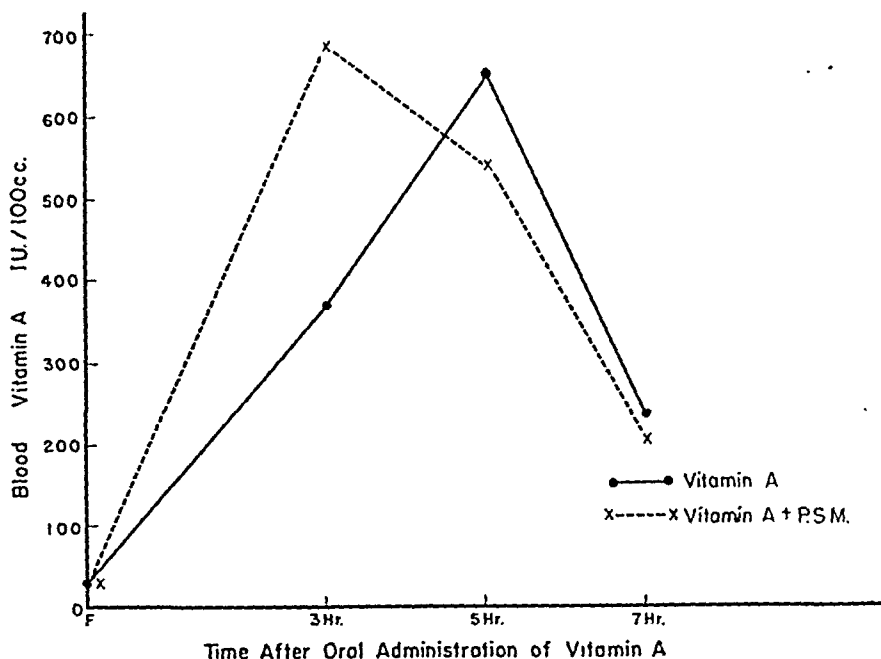


FIG. 1. Composite vitamin A tolerance curves in 16 normal subjects with and without the addition of PSM.

mal individuals. It is apparent, however, that absorption was accelerated after the use of PSM inasmuch as the peak of absorption occurred at about three hours as compared to a peak at five hours in the control studies. In patients suffering from such conditions as subtotal gastrectomy, sprue, pancreatic fibrosis and regional enteritis, similar observations indicate that the addition of PSM to a fatty solution of vitamin A results in important increases in fat absorption. As shown in figure 2, it is evident that in the patients studied, control observations demonstrated a striking interference with fat absorption as shown by low or flat vitamin A tolerance curves. The same patients also gave evidence of their inability to absorb fat normally by the presence of an abnormally high fat content in the stool and by inability to gain weight on ordinary diets. The addition of 2.0 grams of PSM to the test dose of fat-soluble vitamin A resulted in an easily demonstrable increase

in vitamin A absorption, as compared to the original control observations. This increase was outside the error of laboratory technic involved in vitamin A determinations, and in some instances amounted to as much as 400 to 500 per cent of the control peak figures. From these studies, it would seem apparent that the addition of an emulsifying agent (PSM) to a solution of fat-soluble vitamin A accelerated its absorption from the intestinal tract, and in the presence of functional or organic disease of the small bowel, it actually increased the total quantity absorbed.

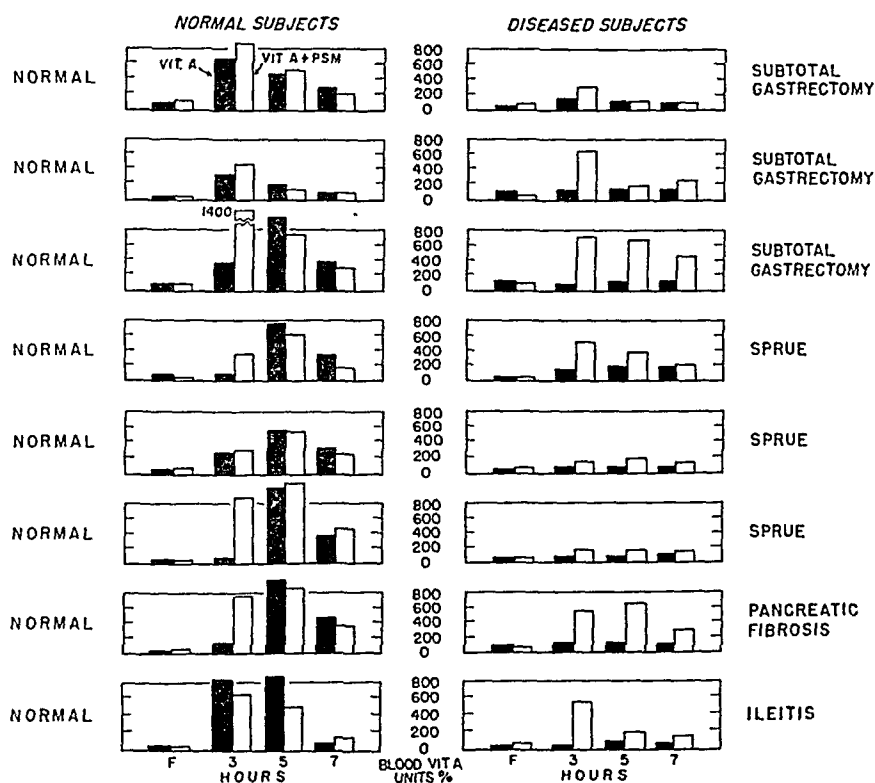


FIG. 2. Comparison of vitamin A tolerance curves in "normal" and "diseased" subjects with oral administration of 200,000 units of vitamin A ester in fish liver oil (black bars) and with 200,000 units of vitamin A ester plus 2.0 grams of PSM (white bars).

In a second set of observations, adequately controlled metabolic studies were made in a group of patients with nutritional difficulties secondary to a subtotal gastrectomy performed for a duodenal ulcer. As already noted, it is not uncommon to find increased quantities of fecal fat after this operation. In a group of four patients, on whom this operation had previously been performed, studies were made on stool fats by the method of Fowweather<sup>7</sup> under control conditions and following the use of various substances that might conceivably increase the absorption of fat from the small bowel. In table 1, it will be noted that no important reduction in the percentage of fecal fat occurred after the use of such substances as desoxycholic acid, folic acid, pancreatic extract, hydrochloric acid, and crude liver extract. In one patient

TABLE I  
Effect of Different Supplements on Stool Fats in Patients Showing  
Malnutrition Following Subtotal Gastrectomy

Case	No. Days Collection Period	Period	Dietary Intake*		Fecal Fat*	
			Fat, Grams	Calories	Grams	% Fat Intake
H. B.	16	Control	107.3	2380	12.6	11.7
	8	Desoxycholic acid 0.3-0.9 gm./ day	107.3	2380	14.2	13.2
	24	Folic acid 10-20 mg./day	107.3	2380	15.0	14.0
P. S.	8	Control	119.0	2620	10.3	8.7
	8	Datein 120 gm./day	119.6	2625	10.0	8.4
	24	Datein + pancreatic extract 15 gm./day	139.5	3295	8.0	5.8
S. K.	12	Control	100.8	2200	18.9	18.8
	12	Pancreatic extract 18 gm./day	100.8	2200	22.7	22.4
	6	Pancreatic + essenamine 100 gm./day	109.7	2720	15.8	14.4
B. G.	16	Control	133.1	2395	7.0	5.3
	16	HCl 12 c.c./day	133.1	2395	10.5	7.9
	8	Crude liver extract 2 c.c./day	133.1	2395	10.5	7.8

\* Daily average.

(S. K.), the addition of a large amount of a lactalbumin hydrolysate to the diet apparently effected a reduction of some importance in the fat content of the stool. In patient P. S., however, no such reduction occurred when a comparable amount of a similar protein was administered over an eight-day period.

Similar observations on four other patients with subtotal gastrectomies were carried out and are summarized in table 2. All four of these patients were badly nourished and had difficulty in doing more than maintain their weight, even with a very adequate caloric intake. In each instance, the percentage of ingested fat lost in the stool was greater than the generally accepted normal maximum figure of 4 per cent. In the last two cases, the amount of fat lost in the stools was 12.4 and 14.6 per cent of the ingested fat respectively. After adequate control periods on an absolutely constant diet, PSM was added with the meals in doses of 1.5 grams three times a day. In each case, after the addition of this emulsifying agent there was a reduction in fecal fat. In the first two cases, this reduction was moderate but definite. In the last two cases, the amount of fat present in the stools after the administration of PSM was approximately only one-quarter of the amount originally found on a control diet. In patient R. S., the experiment was made of doubling the fat intake after control observations had been carried out. It will be noted that when the daily fat intake had been raised from 98 grams to 183 grams, the percentage of fat lost in the stools remained essentially the same, although the total amount of fat lost was practically double. At this point, PSM was again added to the diet, and its use resulted

TABLE II  
Effect of PSM on Stool Fats in Patients Showing Malnutrition  
Following Subtotal Gastrectomy

Case	No. Days Collection Period	Periods	Dietary Intake*		Fecal Fat*		Gastric Portion Resected
			Fat, Grams	Calories	Grams	% Fat Intake	
E. R.	12	Control	103	2900	11.4	11.0	Upper
	12	PSM	103	2900	9.7	9.4	
R. S.	12	Control	98	2325	6.2	6.3	Lower
	12	PSM	98	2325	3.5	3.6	
	12	Control	183	3095	12.7	6.9	
	12	PSM	183	3095	8.2	4.5	
D. B.	6	Control	100	2800	12.4	12.4	Lower
	6	PSM	84**	2350	3.2	3.8	
J. B.	6	Control	100	2995	14.6	14.6	Lower
	6	PSM	100	2840	3.7	3.7	

\* Daily average.

\*\* Patient unable to tolerate such large intake of food as during control period.

in a measurable reduction in stool fats, even though the amounts of dietary fat had been practically doubled.

The findings in Case J. B. are worthy of detailed comment. This patient had an intractable duodenal ulcer, for which elective surgery was indicated. He was admitted to the metabolic ward for control observations prior to operation. The results of these studies are shown in table 3 under "Period I." It will be noted that the percentage of fat lost in the stool during this preoperative control period amounted to 3.2 per cent of 100 grams fat intake. After these observations were made, the patient was operated upon, and a routine subtotal gastrectomy was performed. Twenty-eight days after the operation he was returned to the metabolic ward, and studies were carried out similar to those made before surgical interference. Although the patient

TABLE III  
Study of Fat Absorption in a Patient with Duodenal Ulcer. Comparison of Fat Absorption  
before Subtotal Gastrectomy, 28 Days and 7 Months after Operation, and  
during Administration of PSM

	Period I	Period II	Period III	Period IV
	Pre-Op. Control	28 Days Post-Op.	7 Mo. Post-Op.- Control	7 Mo. Post-Op. Therapy
Average calorie intake	2400	1460	3000	2840
Fat intake (grams)	100	40	100	100
Total fecal solids (grams)	12.6	21.0	29.0	38.0
Total fecal fat (grams)	3.2	10.8	14.6	3.7
Fat per cent dried wt.	26	26	50	10
Stool fat per cent intake	3.2	27	14.6	3.7
Split fat per cent	58	75	82	18
Weight kg. (normal 75)	60.8	56.4	62.5	62.6
			62.6	63.4

was unable to take an equivalent amount of food, it is of interest to note that with a daily intake of only 40 grams of fat, 10.8 grams or 27 per cent of the ingested fat was lost in the stools. Six months later, after the patient had become reasonably well adjusted to the operative procedure, a third period was run with the patient on a full diet of 3,000 calories containing 100 grams of fat. It will be noted that his weight at this time was only 1.7 kilograms greater than his immediate preoperative weight; it was still approximately 13 kilograms under his normal weight. On the above diet, stool fats amounted to 14.6 per cent of the fat intake. At the end of this period he continued under observation on the metabolic ward with practically no change in his diet, the fat content being constant at 100 grams per day. During Period IV, however, he was given 1.5 grams of the emulsifying agent PSM with each of his three main feedings. In two weeks' time the fecal fat had dropped to a figure almost identical with that observed in the original preoperative control period, or one which is well within normal limits.

It would seem from this set of observations that under conditions such as subtotal gastrectomy, in which the absorption of fat from the small bowel is seriously reduced, we have been able to improve fat absorption by the addition of an emulsifying agent to the diet.

A third type of study was carried out on a young woman of 28 years with a diagnosis of sprue, who was followed as an ambulatory patient for a period of a year and a half. The diagnosis was substantiated by the presence of steatorrhea, postprandial abdominal distention, loss of weight, glossitis, and anemia. Laboratory studies showed excessive amounts of fat in the stools and an absolutely flat vitamin A tolerance curve. For a period of nine months her treatment consisted of a regulated diet, limitation of physical activity, and the administration of folic acid. Her diet contained approximately 2400 calories, consisting of 215 grams of carbohydrate, 90 grams of protein, and 130 grams of fat. Folic acid was administered in daily doses of 15 mg. by mouth and was used because the patient was sensitive to any liver extract. Doses of folic acid larger than 15 mg. a day could not be used because of the appearance of headaches, dizzy spells and loss of appetite. On this regimen, the clinical symptoms of the disease were partially controlled, but over the entire nine months' period there was essentially no gain in weight. As will be seen in figure 3, during the first nine months several determinations of stool fat showed a loss in fecal lipids of approximately 22 grams per day, a very excessive fat loss. At the end of nine months, a single addition to therapy was made, namely, the administration of 1.5 grams of PSM with each of the three meals. Actually, the caloric intake was maintained at a slightly lower level, but the fat content was kept at approximately the same level. Folic acid was continued in the same dosage until the last two months, at which time it was discontinued. During this second period of nine months, there was a slow, steady gain of 21

pounds in weight, and there was no diminution in weight gain after the omission of folic acid. The clinical symptoms during this period were almost completely controlled. It is of interest to note that the steady gain in weight was accompanied by progressive diminution of the amount of fat lost in the stools. The final determination of fecal fat loss was approximately 7 grams per day.

Although this therapeutic experiment is subject to the criticism of not being as completely controlled as were those observations made on the metabolic ward, the patient carried out her regimen faithfully and no important modifications of her dietary or medicinal regime occurred. There can be little doubt that the addition of an emulsifying agent to the diet accompanied and probably caused a progressive gain in weight, and at the

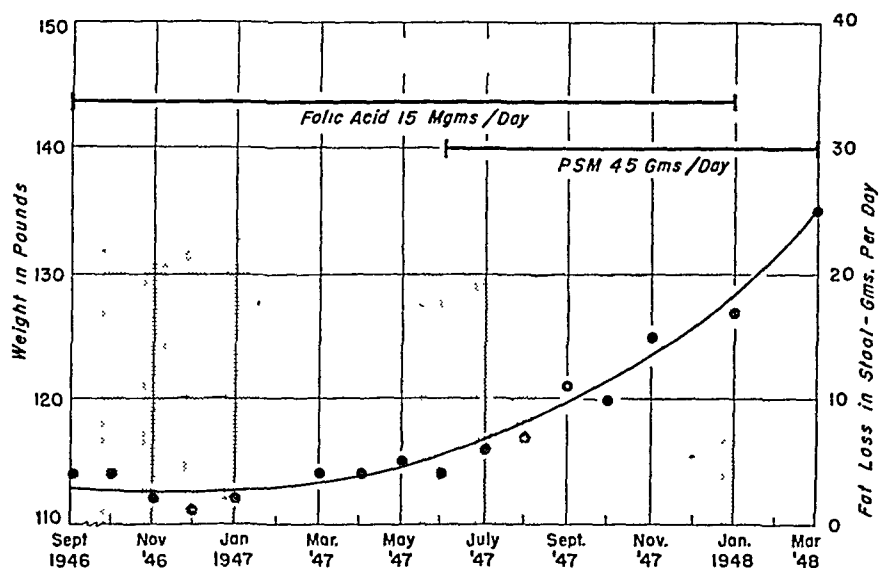


FIG. 3. Weight curve of a patient with nontropical sprue during two 9-month periods; the first on fixed dietary and folic acid therapy only, and the second on the same regimen with the single addition of 4.5 grams of PSM per day. The average fecal fat loss in grams per day at various intervals throughout the period of study is shown by the vertical bars.

same time reduced the fat lost in the stools. It is important to note that in spite of clinical improvement, at the end of this period the patient's vitamin A tolerance curve remained absolutely flat, indicating that the fundamental disturbance of physiology in the small bowel had been unaltered. It is of incidental interest that in this patient with sprue, the addition of PSM to a vitamin A load test changed the tolerance curve from a flat curve to one indicating greater absorption, although it did not rise to normal levels.

### DISCUSSION

From the foregoing experimental and clinical observations, we believe that it has been possible to demonstrate in human beings increased absorption of fat and fat-soluble substances by the addition of an emulsifying agent to



the diet. Although the exact mechanism of action is not known, it is probable that the agent, polyoxyethylene sorbitan monooleate, accomplishes this result because of its ability to lower surface tension. The effect primarily is that of a substance capable of modifying opposing interfaces, with resulting improvement of emulsification, "wetting," spreading or dispersion. Such an agent, by lowering surface tension in the case of dietary fats, undoubtedly increases the total surface area of lipid material to be presented to the intestinal villi by reducing the size of the fat globules. The use of such an agent would seem to represent a new approach to a rather common and difficult therapeutic problem, namely, the control of steatorrhea. In the past, preparations of bile salts have been used with indifferent success in achieving such a therapeutic result. Our studies would lead us to believe that an emulsifying agent, such as polyoxyethylene sorbitan monooleate or some other similar agent, may be of real value in effecting an improvement in the absorption of fats or fat-soluble substances from the small bowel in conditions where absorptive difficulties constitute a problem of major clinical importance. Under normal physiological conditions, the absorption of dietary fat from the intestinal tract is so nearly complete that the addition of such an agent to the diet would seem to be of negligible value. Although confirmatory data are not yet available, it is possible that the use of an emulsifying agent may exert an appreciable influence on the absorption of other substances than fat. In conditions of serious malnutrition secondary to such disturbances as celiac disease, sprue, chronic inflammatory diseases of the jejunum or ileum, anastomotic operations of the upper gastrointestinal tract, and the like, the utilization of such a therapeutic measure may promise significant clinical benefit.

#### BIBLIOGRAPHY

1. WOLLAEGER, E. E., COMFORT, M. W., and OSTERBERG, A. E.: Total solids, fat and nitrogen in the feces. III. Study of normal persons taking a test diet containing a moderate amount of fat; comparison with results obtained with normal persons taking a test diet containing a large amount of fat, *Gastroenterology*, 1947, ix, 272.
2. WOLLAEGER, E. E., COMFORT, M. W., and WEIR, J. F.: The total solids, fat and nitrogen in the feces. II. Study of persons who had undergone partial gastrectomy with anastomosis of entire cut end of stomach and jejunum (Polya anastomosis), *Gastroenterology*, 1946, vi, 93.
3. DUBOS, R. J.: Rapid and submerged growth of mycobacteria in liquid media, *Proc. Soc. Exper. Biol. and Med.*, 1945, lviii, 361.
4. KRANTZ, J. C.: Personal communication.
5. KRANTZ, J. C., CULVER, P. J., JONES, C. M., WILCOX, C. S., and ROSE, R. S.: Paper in preparation.
6. MAY, C. D., BLACKFAN, K. D., MCCREARY, J. F., and ALLEN, F. H., JR.: Clinical studies of vitamin A in infants and children, *Am. Jr. Dis. Child.*, 1940, lix, 1167.
7. FOWWEATHER, F. S.: Determination of amount and composition of fat of feces. I. Investigation of "wet" method and comparison with "dry" method, *Brit. Jr. Exper. Path.*, 1926, vii, 7.

# HEART FAILURE: THE RELATION OF SYMPTOMS AND SIGNS TO ITS SEVERITY AND DURATION\*

By WILLIAM DOCK, M.D., F.A.C.P., *Brooklyn, New York*

WHEN the estimation of arterial pressure became a routine clinical method, it was at once noted that in cases of congestive heart failure, or cardiac decompensation, arterial pressure often remained abnormally high up to the time of death. Indeed, Sahli noted that in some patients a rise in arterial pressure occurred with the development of failure and that a fall resulted from treatment successfully directed to restoring cardiac compensation.<sup>1</sup> It also was apparent on the most superficial study of elderly patients with heart failure precipitated by Graves' disease that the total volume flow of blood under basal conditions must be considerably greater than normal, for these patients had warm skin and extremities, a bounding pulse, vigorous precordial impulses and loud heart sounds even when edematous and orthopneic.

These facts did not lead the early students of heart disease to question the concept that the condition known as congestive failure was due to failure of the myocardium to meet the demands imposed upon it by the needs of the body for arterial blood. For it is obvious even in cases with increased output and arterial pressure that the load borne by the heart under basal conditions is far less in cases of heart failure than that borne by the normal heart successfully during hours of sustained physical exertion, especially in those many asymptomatic hypertensives who are capable of vigorous and prolonged effort. Cardiacs were found to be incapable of such exertion, and it was assumed that this was due to a decline in the capacity for work in the failing heart.

In the spring of 1947, several of the most experienced investigators, in discussing elevated cardiac output during episodes of failure, urged that the current concept of heart failure was incorrect, for how could an organ be failing if it was doing more work than normal? Such arguments indicate that the whole problem of functional failure must be widely misunderstood, or that the term "failure" as used in medicine requires a definition in a new and stricter sense. The opponents of the old use of "heart failure," as applicable to cases with high basal blood flow or arterial pressure, gave no new definition and merely offered an agnostic attitude toward the problem. This point of view does not lack authority; it was advanced by recognized authorities in cardiac investigation.<sup>2</sup>

In every clinical field, failure of function is assumed to occur more readily under a heavy load than under a basal one, and failure of function leading

\* Received for publication November 1, 1947:

From the Department of Medicine, Long Island College of Medicine, Brooklyn, N. Y.

to serious impairment of health often is seen when the organ is performing more work per day than is necessary to maintain life under basal conditions. It is natural to assume, as most physicians have, that the seriousness of the consequences of any degree of organic failure varies with the load imposed by the body's needs under basal conditions and by the stresses imposed by activity.

For example if a chronic nephritic has been on a normal diet, with 75 gm. of protein per day, and has had a urea output of 24 gm. a day with a constant blood urea level of 125 mg. per cent it is quite probable that he has been free of symptoms. A normal person, on such a diet, excretes 24 gm. of urea daily but has a blood urea of only 25 mg. per cent. If the nephritic's diet is altered, or if severe febrile illness sets in, his protein break-down may rise to 250 gm. per day. If he were normal in his renal capacity for excretion, he would then eliminate 80 gm. of urea a day with a blood level of 70 mg. per cent. But the nephritic's blood urea will rise to 300 mg. per cent before excretion reaches 80 gm. per day, and this may well precipitate severe and even fatal manifestations of uremia. Before death occurs urea excretion may be more than twice the normal level per day, but no physician would suggest that renal failure was not present simply because the imposed load, and the work actually accomplished, were greater than normal.

If such a nephritic had been on a rice diet, with liberal intake of salt and water, the urea excretion might have fallen to 4 gm. a day, and the blood urea to 30 mg. per cent. The normal subject, on such a diet, would have a similar low urea output and a blood level of 8 mg. per cent. No one would suggest that this normal subject was in renal failure because, on a very light load, his kidneys excreted only one fifth the "normal" quantity of urea, or that the nephritic had regained normal renal function because his blood urea now was in the "normal range."

The relations of load, work capacity, and evidence of failure are the same in heart failure as in renal failure. A normal man can have a basal output of 4 liters of blood per minute. During vigorous sustained effort output may rise to 20 liters with little or no increase in the size of the roentgen silhouette of the heart. After a month of starvation, output may have fallen to 2 liters per minute and the roentgen silhouette become much smaller. The cardiac, on the other hand, might have the same basal output, and a roentgen silhouette twice as large, and on starvation might have the same fall in output to 2 liters and a decrease in heart volume to about the size of a normal heart in a person leading an active life on a 2500 calorie diet. If the cardiac happens to have Graves' disease, or anemia with a 60 per cent fall in hemoglobin, his basal cardiac output may be 8 to 10 liters per minute. If such a patient is subjected to conditions which would raise the output of the normal heart to 20 liters, severe disability or even death may occur.

Evidently it is not safe to test the functions of failing organs by forcing them to carry loads which are of value in testing the capacity of normal

organs, and it is not possible to test functional capacity merely by determining the work done under basal conditions, or when work has been brought to minimum levels by diet or starvation. The degree of failure is estimated by obtaining data on the conditions under which the organ manages to perform its work. In the case of the kidney the capacity for function can be measured with great precision by comparing the rate of excretion of one of the metabolites with the plasma content of that substance. Thus the Addis urea ratio, the Rehberg creatinine test and the clearances of inulin, thiosulfate, diodrast or para-aminohippurate give an index of the way the kidney is working. In normal subjects it is necessary to give fluid and raise the blood level of the metabolite in order to get constant values, but when urine specific gravity is fixed and blood levels are elevated by renal failure, no such "loading" may be necessary. The blood levels alone give a rough index of capacity, since the rate of creatinine excretion varies little, and on normal diets even urea excretion varies only between 20 and 60 gm. per day. If creatinine is over 2 mg. per cent (twice the normal level), or urea over 100 mg. per cent (three times the usual level), the kidney is not working properly.

In the liver, function can be judged by comparing the blood levels and rates of excretion of bilirubin, bromsulfalein, rose bengal, etc. In the heart and in the hollow viscera, motor function can be judged by the amount of content moved and the volume of the viscus at the end of a phase of active movement. Thus, the volume of gastric content seven or twelve hours after a standard meal, of the urinary bladder at the end of micturition, and of the heart at the end of systole, serve as indices of the capacity for motor function.

Some species of mammals have almost no blood in the ventricular chambers at the end of systole under basal conditions of flow, but in man the heart volume at the end of systole is greater than that of the empty heart. Normally its volume with the ventricular content at the end of systole is 30 to 60 per cent greater than the volume of the myocardium, but with the low cardiac output and blood pressure of acute hemorrhage the volume may be only 5 or 10 per cent greater than if it were completely empty. In heart failure the volume of the ventricles, at the end of systole, may be 300 to 500 per cent greater than the volume of the empty heart. In a normal person increase in cardiac output evoked by rapid intravenous infusion of saline raises the volume of the ventricular content well above the basal figure.

Myocardial efficiency, as Starling proved in animal experiments, can be measured by comparing the ventricular volume with the work per beat, just as renal function is measured by comparing the blood level of a metabolite with its rate of excretion. At normal rates of contraction, the energy liberated and the oxygen required by the heart are proportional to its diastolic volume. In normal subjects accurate estimation of cardiac efficiency can be made only by raising the mechanical work well above the basal level. This can be done safely, when the roentgen silhouette is normal in size under basal

conditions, by massive intravenous infusion of saline. However, once the heart volume under basal conditions is abnormally large, the function of the organ can be evaluated by studies made without additional loads of work; and such test loads as may be imposed in normal subjects may lead to discomfort and danger in those with failing hearts.

In normal subjects the cardiac output and the systolic pressure rise following epinephrine or effort, but the cardiac silhouette may remain unchanged, may increase or decrease in area. Vasodilatation in muscles, increase in rate, and perhaps metabolic effects of the procedure increase the efficiency of systolic contraction so that the stroke volume rises slightly and minute volume increases greatly with minimal change in volume of the heart. Epinephrine and effort may have similar effects in early heart failure, when symptoms at rest occur only on recumbency, and heart volume is but moderately increased. Under these circumstances effort may be well tolerated but intravenous infusion at rapid rate may markedly dilate the heart and precipitate severe pulmonary edema. Hence the loss of function in dilated hearts must be calculated under basal conditions, and not during effort or infusion. By using diodrast angiography to visualize the heart chambers and the catheter to measure cardiac output and pulmonic arterial pressure, the clinical physiologist can obtain all the data necessary to calculate ventricular efficiency, using work and diastolic ventricular volume. This is no more inconvenient to the patient, or arduous for the investigator, than catheterizing a ureter and measuring minute output and blood levels of a metabolite such as creatinine in order to calculate the function of either kidney. Such precise measurements are of value to the physiologist but they have no place in clinical medicine except in laboratories where fundamental problems in clinical science are being studied.

Clinically, failure may be defined as a loss of organic function sufficient to produce symptoms apparent to the patient, or signs apparent to the unaided eyes of a trained observer. The greater the loss of function, the less the load necessary to evoke symptoms or signs. When symptoms or signs are apparent with loads of work less than the minimal level observed in normal subjects, the loss of functional capacity in the heart, liver, kidneys, or pancreatic islets probably is over 90 per cent. Symptoms may occur, if the load is two to five times the normal basal level, when loss of function is more than 50 per cent. A cardiac with beriberi or Graves' disease, who is not entirely comfortable at rest and recumbent, has probably suffered a decrease of about 80 per cent in cardiac function, and is in heart failure with an output twice normal.

The heart, liver and kidney may fail because of intrinsic disease, or because the flow of blood into the organ is insufficient. Here we refer not to the blood which nourishes and supports the organ, but the blood on which it performs a mechanical or metabolic function. In the case of the liver, diversion of the portal flow may raise oxygen tension in the organ while

reducing its functional capacity. In the heart the flow of blood into the chambers is independent of that to the muscle, and failure of the circulation may occur if high pericardial tension, low pressure in the venae cavae or shortening of diastole due to excessive rise in rate (paroxysmal tachycardias over 200 per min.) prevent normal diastolic filling. It is best to describe such a state as circulatory failure due to shock, hemorrhage, tachycardia, tamponade, constrictive pericarditis, or whatever, so as not to confuse it with congestive heart failure due to loss of myocardial function. In the kidney, vasoconstriction and decline in cortical metabolism set in early in shock or hemorrhage, so that renal function may decrease and blood urea rise in the absence of organic renal disease or serious circulatory defect in other vital organs. This, then, should be called circulatory renal failure.

In the healthy young adult, with no myocarditis, the myocardium can sustain for long periods the labors imposed by valve lesions, high basal rates of flow, hypertension and a vigorous way of life. Often this is possible with no increase in heart volume. On the other hand, the aging heart may dilate and fail even though the patient is sedentary, the blood pressure and cardiac output at low normal levels. Between these extremes of compensation and decompensation is the great range of patients with varying degrees of overloading and of loss of function of the ventricular muscle. In the management of each case, the variations in heart volume, in symptoms and in signs, from time to time and in relation to therapy and activity, are of far more importance than precise measurement of ventricular efficiency on any one date.

McMichael and his co-workers have clearly defined the significant differences, in etiology, prognosis and therapy between failure associated with low or normal basal levels of cardiac output, and that associated with high output.<sup>3</sup> The former can be recognized clinically by the coolness of the extremities and skin, and by a low pulse pressure in the absence of murmurs of aortic valve disease. Since pulse pressure, at any given stroke volume, rises with the diastolic pressure, hypertensive patients have a relative, and not an absolute, decrease in pulse pressure.

But increase in cardiac output is not the only cause of increased load on the ventricles, even if it is the most significant one in precipitating failure. The level of the systemic arterial pressure must be considered in its relation to left ventricular failure, the loud pulmonic second sound present in pulmonic hypertension must be considered in cases of right ventricular failure, and murmurs diagnostic of valvular stenosis or incompetence, or of arteriovenous shunts must be borne in mind when estimating whether overloading under basal conditions is present even though the cardiac output is normal or less than normal. These are the factors which, with the heart volume seen by roentgen-ray and the signs and symptoms of failure, are used to evaluate the relative degrees of myocardial failure and of overloading which are present.

Because heart failure is primarily an example of muscular fatigue associated with incomplete recovery of the ventricle in diastole, any increase in rate of beat or shortening of diastole diminishes the capacity for work by the myocardium. Even in young people, prolonged tachycardia, with normal or reduced arterial pressure and minute volume flow of blood, leads to dilatation of the heart; in older ones failure is often precipitated by rise in rate due to arrhythmia. Disturbances of intraventricular conduction, which prolong systole and shorten diastole, also predispose the heart to fail even though work per beat and rate per minute remain normal. Therefore, the clinician evaluates the state of the myocardium from the apparent degree of failure and the rate of beat. The slower the rate and the more normal the duration of the QRS complex of the electrocardiogram, the more severe must be the damage to the myocardium to precipitate failure of any given type and severity. If the rate is rapid, and the QRS, because of injury to the Purkinje fibers, is over 0.14 second, failure may occur which completely clears up at normal rates and with normal conduction time, thus proving the anatomic and enzymatic integrity of the myocardium.

In heart failure systole is prolonged.<sup>4</sup> When the QRS is not over 0.08 second in duration, increase in the quotient given by dividing duration of systole by the duration of the cycle is regularly associated with other evidence of failure. An altered form of the ballistocardiogram also results from failure and prolongation of systole. Gallop rhythm, bizarre ballistocardiograms, and prolonged systole, if encountered in patients with normal duration of QRS, serve as objective proof that the myocardium is inflamed, fibrosed, or suffering from some metabolic dysfunction. The functional capacity has been reduced, and usually some degree of dilatation is present in such instances.

So far nothing has been said concerning venous pressure or circulation time. Venous pressure in the neck can be judged by inspection as the patient is shifted from recumbent to sitting and the level of venous engorgement above the heart is observed. Direct measurement can be made from an arm vein or with the catheter in the right auricle. The pressure depends on the degree of cardiac failure and on the load imposed on the heart, as well as on the average level of intrathoracic pressure. When respiration changes from gasping to grunting the intrathoracic pressure, and with it the venous pressure, rise 3 to 8 cm. of water, and the cardiac output falls. The observed pressure must be correlated with the type of respiration, degree of emphysema, pulse pressure and coldness of the finger tips to permit an estimation of cardiac output in relation to right auricular pressure.

Circulation time depends on volume of the heart chambers, on degree of venous engorgement, and on the minute volume flow.<sup>5</sup> The velocity of flow may be relatively high, arm-to-lung or arm-to-tongue time relatively brief, in patients with high output failure (beriberi, Graves' disease, high fever, severe anemia, arteriovenous fistulae, Paget's disease of bone, etc.). Neither

venous pressure nor circulation time is an accurate index of myocardial efficiency.

The relation of venous pressure to heart failure has been misunderstood and there has been confusion about the relation of venous pressure to edema. In mitral stenosis it is usually, and we think correctly, assumed that the rise in pulmonic arterial pressure is secondary to a rise in pulmonic venous pressure. The arterial pressure in these cases has been measured by the catheter method and found to be 60 to 120 mm. Hg, the normal 15 to 30. One who ascribed edema solely to high venous pressure would scarcely believe that no clinical evidence of pulmonary edema and no hydrothorax might be found in many such patients, but this is a well-known clinical fact. Even after right heart failure has set in and the liver is enlarged, the lungs of a mitral stenosis case may be free of râles. No one doubts that high venous pressure is, and for years has been present in the lungs of such patients, or that pulmonary edema can develop rapidly in certain types of acute left ventricular failure. Edema usually does not develop when venous pressure rises gradually, as in the lungs with mitral stenosis or in the legs and ankles of young people when they grow up and the column of blood between the ankles and the heart reaches a height of 100 cm. or more. Whether this freedom from edema is due solely to vascular thickening with rise in pressure, or is aided by increased flow of lymph, has not been determined. It is important to recognize that edema may be entirely absent in severe chronic venous hypertension, but occurs readily with acute episodes of moderate rise in venous pressure. Rate of change in conditions, rather than degree of change, often explains the severity of symptoms in many types of organic failure. Rate of development of failure often explains not merely severity, but the actual character of the symptoms.

Unless the kidneys fail suddenly and completely (i.e. acute anuria or oliguria) there will be no symptom due to "forward" failure of urine flow. In the chronic disorders anuria is only an agonal event. This is also true in the heart; symptoms similar to those of shock only occur when the heart is suddenly and very severely injured, or its filling suddenly impaired by tachycardia or by tamponade. Then a weak or impalpable pulse may result, and weakness, sweating, loss of consciousness, anuria and paralytic ileus may occur. Except with myocardial infarct or massive pulmonary embolism actual myocardial failure rarely develops suddenly. Even when these accidents precipitate acute failure with symptoms of shock ("forward failure"), if the patient survives a few hours compensatory changes set in and the usual signs of congestive failure—rise in venous pressure, pulmonary edema, hepatic swelling and tenderness—appear.

The first evidence of these compensatory changes is a rise in systemic venous pressure, in cases of pulmonary embolism, and the development of râles in the caudal, dorsal lung fields in myocardial infarction or rupture of an aortic or mitral leaflet. In vigorous young men the normal blood volume



is relatively large and these signs may develop rapidly even when the sudden injury produced few or no symptoms of shock or "forward failure." In elderly sedentary patients this rarely occurs, because, with average levels of blood volume the rise in venous pressure due to sudden heart failure, with the output of one ventricle markedly embarrassed, is not sufficient to produce symptoms and signs in the first few minutes, or even in the first few hours. Such clinical observations confirm Welch's classic studies on the difficulty of producing acute pulmonary edema in dogs by clamping off the aorta or a large part of the left ventricle. High venous pressures are due not to "backward failure" but to the physiologic responses to a reduction in blood flow below the optimal level in all the tissues of the body. This is why congestive failure, in its most advanced form, can be seen in patients whose basal cardiac outputs are well above normal, but insufficient to meet the abnormal tissue needs created by anemia, lack of thiamine, or excess of thyroglobulin, or the abnormal circulatory conditions due to arteriovenous shunts. Those who have likened "backward failure" to the condition in Harvey's celebrated experiment, in which the snake's aorta was ligated and its venae cavae became tense and swollen, have ignored the fact that congestive heart failure often is severe even though the heart is moving more blood per minute than it does in normal resting subjects. The anasarca, the high venous pressure, the greatly increased volume of plasma and red cells in the body—in a word, all the characteristic features of chronic heart failure—are due, not to the heart's damming back blood, but to a discrepancy between the optimal flow to the tissues, and the flow provided by the failing myocardium.

In acute failure this discrepancy may be severe enough to produce syncope without causing pulmonary edema; in chronic failure it causes all the changes just noted, even though no fall in arterial pressure and no decrease in blood flow to the brain and heart have resulted. The earliest response to a decrease in cardiac output is a rise in venomotor and vasomotor tone, which restores arterial pressure and helps to maintain cardiac filling. But only in vigorous young people, whose blood volumes are relatively high from constant strenuous activity, is the resulting shift of blood from the periphery to the great veins and the thorax sufficient to cause an immediate distention of neck veins or pulmonary edema as a result of acute heart failure.

When decrease in cardiac output is due to shock or hemorrhage, the immediate effect of changes in the tone of venules and arterioles is to bring venous pressure back toward normal, and to shift the balance of fluid exchange between blood and tissues toward the intravascular side. Thus, blood volume tends to increase by hemodilution, unless the patient is dehydrated. In acute cardiac failure, with a rising venous pressure, increase in blood volume occurs more slowly, and it is only after days or weeks of failure that the blood volume rises to levels sufficient to cause intense engorgement of the viscera and the great veins. This rise in blood volume, and therefore all the usual manifestations of congestive failure, are thus sequelae of a low

cardiac output, just as is the replacement of blood volume after a donation to a blood bank. Sodium retention and fluid retention are effected through changes in activity of the hypothalamic, and hypophyseal-adrenal cortical mechanisms. They are facilitated by the decrease in renal blood flow which is the first response to reduced cardiac output. These changes in renal blood flow, in sodium excretion and in blood volume all occur in normal subjects kept in the upright position, which in itself reduces cardiac output by trapping blood in the distended veins below the diaphragm and thus reducing cardiac filling.<sup>6</sup> Increase in blood volume may also be mediated through the nervous system, since polycythemia has been observed with cerebellar tumors, or this may be due to vasoconstriction in vessels supplying the liver and the bone marrow. Whatever the mechanisms involved, red cell and plasma volume atrophy in heart failure just as they do after hemorrhage. Retention of salt and water lead to edema, which is most apparent in the sites where tissue pressures and pulse pressure are low and venous pressure high.

It is now apparent that the rise in arterial pressure in heart failure, first noted by Sahli, and all the classical features of congestive failure are due to the fact that mammals have developed a complex and effective mechanism for dealing with the decrease in cardiac output occurring in shock, hemorrhage and dehydration, and that this mechanism comes into play whenever the cardiac output is reduced for any reason whatever. Without such a mechanism heart failure would result only in fatigability, or if severe, in anuria, abdominal distention, weakness and syncope. The mammal evolved no reflex mechanism for dealing with myocardial failure as such, for the obvious reason that wild animals do not have heart failure during the normal reproductive life span. In civilized man the development of congestive failure is hastened by the high salt content of the diet, which makes possible rapid increases in blood and intercellular fluid volume, and by alternation between an erect posture, which diminishes cardiac output, and recumbency, which allows blood and edema fluid in the legs to be mobilized and pile up in the lungs.

All of the classical symptoms of congestive heart failure can be relieved by bleeding and by use of mercurial diuretics and salt restriction, which deplete the extra-cellular fluid reservoir and eventually lower blood volume and venous pressure. In some cases these symptoms can be relieved by trapping blood in the limbs by tourniquets or cuffs under suitable tension. Digitalis, which increases myocardial efficiency, also diminishes the venous return. If the heart has been filled at auricular pressures above the optimal, all these procedures, as McMichael has shown, may increase rather than diminish cardiac output. However, in high output failure, symptoms are marked before myocardial inefficiency has reached a point at which rise in venous pressure reduces cardiac output. In such cases, this type of treatment will lower cardiac output. Should the output fall critically as a result of bleeding

or digitalization, syncope, extreme weakness and death may occur even though venous pressure is still abnormally high, and cardiac output higher than in a case of low output failure prior to effective therapy. For when metabolic, hemic, or shunt-like vascular defects raise the need for minute volume flow for the whole body, a reduction in venous filling can not be compensated and a shock-like condition sets in. The brain and heart, robbed by the increased flow to other tissues, may then be irrevocably damaged as the cardiac output falls to or below the normal basal minute volume.

### SUMMARY

The term "heart failure" should be applied only to the clinical disorder which is due to inability of the myocardium of the ventricles to maintain the *requisite* flow of blood to all the tissues of the body. "Circulatory failure" should be used for those conditions in which requisite flow is not maintained, in spite of an adequate myocardium, because shock, hemorrhage, pericardial tamponade, constrictive pericarditis, or extreme rates of tachycardia prevent adequate diastolic filling of the ventricles. Both heart failure and circulatory failure can be acute (minutes or hours), subacute (days) or chronic (weeks to decades). Shock and hemorrhage produce only the acute form. In acute failure, whether myocardial or circulatory, the pulse is diminished, blood pressure may fall, and weakness, syncope or anuria may follow. In the chronic form of either type of failure, there are rarely any of these phenomena, but instead venous distention and congestion of the lungs or liver dominate the clinical picture.

In heart failure the basal cardiac output of blood, the pressure in the pulmonic artery or the aorta, or the work of one ventricle in cases of an insufficient valve, may be above normal almost until death. The measure of the loss of efficiency of a ventricle is given by the decrease in the quotient of the formula: ventricular work divided by diastolic ventricular volume. Clinical estimation of the loss of efficiency can be made from the signs of increased cardiac work and from the heart size as seen under the fluoroscope. The signs and symptoms of congestion in the lesser and greater circulation are secondary to failure of the heart to supply the tissues adequately with blood. They provide an index of the severity and duration of failure of the tissues to be adequately perfused, but can not be interpreted as measures of, or even evidence for, myocardial failure.

The basal cardiac output is not necessarily reduced in myocardial failure, and in many cases the increase in cardiac output which is present has precipitated heart failure with a relatively high level of cardiac efficiency, just as a high protein intake precipitates ur mia with relatively competent kidneys.

## BIBLIOGRAPHY

1. SAHLI, H.: Herzmittel und Vasomotormittel, Verhandl. deutsch. Kong. f. inn. Med., 1901, xix, 45-54.
2. BURWELL, S., and DEXTER, L.: Cardiac output in a case of beriberi, Trans. Assoc. Am. Phys., 1947, lx, 59-64.
3. McMICHAEL, J.: Circulatory failure studied by means of venous catheterization. Advances in Internal Medicine, Interscience Publishers, New York, 1947, ii, 60-101.
4. TARAN, L. M., and SZILAGYI, M.: Duration of electrical systole in acute rheumatic carditis in children, Am. Heart Jr., 1947, xxxiii, 14-26.
5. NATHANSON, M. A., and ELEK, S. R.: The influence of heart size on circulation time, Am. Heart Jr., 1947, xxxiii, 464-476.
6. BRUN, C., KNUDSEN, E. O. E., and RAASCHOU, F.: Kidney function and circulatory collapse, Jr. Clin. Invest., 1947, xxv, 568-574.

# THE SHOULDER-HAND SYNDROME IN REFLEX DYSTROPHY OF THE UPPER EXTREMITY \*

By OTTO STEINBROCKER, M.D., *New York, N. Y.*, NORMAN SPITZER, M.D., *Yonkers, N. Y.*, and H. HAROLD FRIEDMAN, M.D., *Denver, Colorado*

A VARIETY of seemingly unrelated clinical disorders, usually considered distinct entities, have been described in the surgical and medical literature for many years. These conditions include causalgia,<sup>1, 2, 3</sup> Sudeck's atrophy (post-traumatic osteoporosis),<sup>4-12</sup> painful disability of the shoulder following coronary occlusion,<sup>13-19</sup> post-infarctional sclerodactylia,<sup>20</sup> palmar and digital contractures as well as Dupuytren's contracture,<sup>21-26</sup> the swollen atrophic hand associated with cervical osteoarthritis,<sup>27</sup> certain changes in the paretic limbs of hemiplegics,<sup>27-32</sup> and a number of others. In this group belongs the idiopathic shoulder-hand syndrome.<sup>33</sup> It is becoming increasingly apparent that, although the etiology of these various syndromes may be different, many of their clinical features, and probably the neurovascular mechanisms underlying their development, are very similar, if not identical.<sup>34, 35</sup>

Certain clinical features common to these disorders have been termed reflex dystrophy by de Takats.<sup>13-16</sup> This designation refers chiefly to the characteristic vasomotor and trophic disturbances in the affected extremity provoked by an etiologic factor through neurovascular reactions. The vasomotor and trophic symptoms usually are presumed to arise from reflex stimulation of the sympathetic nerve supply. Some authors, accordingly, add "sympathetic" to the term as in "reflex sympathetic dystrophy." The interpretation of the underlying mechanism in these diseases largely represents a clinical presumption supported by an abundance of empirical material. Even with the present incomplete knowledge of these disorders the use of the term "reflex dystrophy" is warranted as a working basis.

The most recently described clinical picture which must be regarded as a form of reflex dystrophy is the shoulder-hand syndrome, particularly the idiopathic variety, reported by one of us (O. S.).<sup>33</sup> This condition consists of a peculiar combination of painful shoulder disability with homolateral pain and swelling of the hand described in six otherwise healthy adults, seen over a period of nine years.<sup>33</sup> In five of the patients the swelling of the hand was followed by trophic changes. Owing to the absence of any history or evidence of preceding trauma or associated disease these cases were presented as the "idiopathic" manifestation of the disorder. The clinical picture and course in the idiopathic variety resemble those produced by the different etiologies to be considered later<sup>33</sup> (figure 6). The recognition of this com-

\* Received for publication October 8, 1947.

From the Arthritis Clinic and Medical Service, Fourth Medical Division (New York University), Bellevue Hospital.

Aided by a grant from the Robert Trubek Rheumatism Fund.

bination of shoulder and hand symptoms as the expression of the same disorder, whatever its origin, rather than as a coincidental involvement of the shoulder and hand by unrelated causes must be stressed.

TABLE I  
Reflex Dystrophy of the Upper Extremity

Clinical Forms

- A. Incomplete (Abortive)
  1. Contractures of the palmar fascia and Dupuytren-like contracture.
  2. Painful vasospasm or vasodilatation of the hand.
  3. Swelling and atrophy of the hand.
  4. Painful disability of the shoulder.
- B. Complete
  1. The shoulder-hand syndrome.

The present report is based on a study of 42 cases of reflex dystrophy of the upper extremity followed for periods of one month to nine and one-half years. Thirty-six of these patients presented the shoulder-hand syndrome due to a variety of causes or associated factors shown in table 2.

TABLE II  
Etiologic Varieties of Reflex Dystrophy of the Upper Extremity  
(the Shoulder-Hand Syndrome) in Our Series

- A. Idiopathic
- B. Peripheral Lesions
  1. Trauma and suppuration of the extremity (Sudeck's atrophy, causalgia, post-traumatic osteoporosis, acute bone atrophy).
  2. Vascular disease (thrombophlebitis, diffuse vasculitis, periarteritis nodosa).
  3. Intraforaminal osteoarthritis of the cervical spine (Oppenheimer).
  4. Cardiac disease—post-infarctional.
  5. Other thoracic diseases (post-pneumonic, etc.).
  6. Nodular panniculitis (Weber-Christian).
- C. Lesions of Cord and Ganglia
  1. Herpes zoster.
  2. Diffuse vasculitis?
- D. Higher Lesions
  1. Cerebral lesions (hemiplegia).

From our studies and a survey of the literature it seems plain that reflex neurovascular dystrophy may be provoked by many agencies, but the variations in its manifestations have led to some confusion perpetuated by the multiplicity of its clinical descriptions and designations. It may be useful, therefore, to coördinate the many closely related conditions obviously belonging in this category and differing chiefly in etiology or in minor clinical details.

The subject may be further clarified by regarding the variable clinical features as expressions of the different degrees of reflex neurovascular and motor response to provocative internal or external agents. Although the most extensive clinical picture of reflex dystrophy of the upper extremity is embodied in the shoulder-hand syndrome, certain characteristic signs may be absent in some cases. We have found too that, during its development in some patients, reflex dystrophy evidently may be arrested by treatment, with or without residual changes. It may undergo spontaneous partial or

complete resolution, however, at any stage, again with or without persistent alterations. We have come to recognize, therefore, certain incomplete or abortive forms to be described, as well as its typical, most severe evolution as the shoulder-hand syndrome as listed in table 1.

Reflex neurovascular phenomena usually arise as a complication of some primary condition. In many of these instances the superimposed reflex disorder, by the severity of its symptoms or its inevitable and disabling progression, may rapidly overshadow the underlying cause in diagnostic and therapeutic importance.

Reflex dystrophy occurs in the face, lower extremities and spine, but we are concerned here only with its development in the upper extremity.<sup>4, 34</sup>

### WHY "THE SHOULDER-HAND SYNDROME"?

The need for segregating one pattern of reflex neurovascular dystrophy as a special entity deserves some consideration. The upper extremity is provided with a relatively rich network of sympathetic communications. There is a more or less indirect but intimate relationship between the thoracic viscera and the upper limbs, the brain and the musculoskeletal structures of the upper part of the body, mediated through the abundant autonomic nerves and ganglia of the cervico-thoracic area. Disease in these parts appears to express itself more frequently than is appreciated by reflex neurovascular symptoms in the upper limb.

For some reason we have not observed, so far, any set of reflex phenomena in the lower extremities analogous to the shoulder-hand syndrome. Moreover, the lack of previous correlation of the shoulder and hand involvement as signs of the same disorder in the cases seen by us, as well as in the most recent literature, seems to require the use of a term which crystallizes the chief features of the condition.

The emphasis on the unity of the shoulder and hand symptoms conferred by a special term may stimulate more frequent and earlier diagnosis as well as more rational, less strenuous therapeutic measures than have been reported even in the latest studies.

### CLINICAL COURSE OF THE SHOULDER-HAND SYNDROME

Diagnosis of the shoulder-hand syndrome can be facilitated by a clear-cut understanding of the usual progress of this disorder. It passes through several stages in each of which the signs resemble different diseases. The syndrome may be divided roughly but conveniently into three stages, or phases, according to the observations made on our patients.<sup>8</sup> Sometimes overlapping of symptoms is observed in the various stages, and the duration of these phases may vary somewhat from the time intervals stated.

The *first stage* (figures 1, 6), which usually lasts three to six months, consists ordinarily of the appearance of painful shoulder disability followed by swelling, pain and stiffness of the hand and fingers. The onset may be

gradual or sudden. Complaints may arise first either at the hand or shoulder followed by symptoms at the other location, or both parts may be affected simultaneously. Pain and limitation of motion develop at the shoulder girdle with diffuse tenderness there, very much as in periarthrititis or bursitis. The swelling of the hand and fingers is uniformly distributed and, as a rule, yields little or no pitting to pressure, although in acute onsets



FIG. 1. Phase 1. Painful disability of left shoulder five months, swelling of left hand nine weeks.



striking pitting may be encountered at times. The skin of the hand and fingers becomes smooth and taut, so that the normal wrinkles and creases become shallow or obliterated. Degeneration and desquamation of the superficial layers of the cutis, to a lesser degree on the forearms, occurred

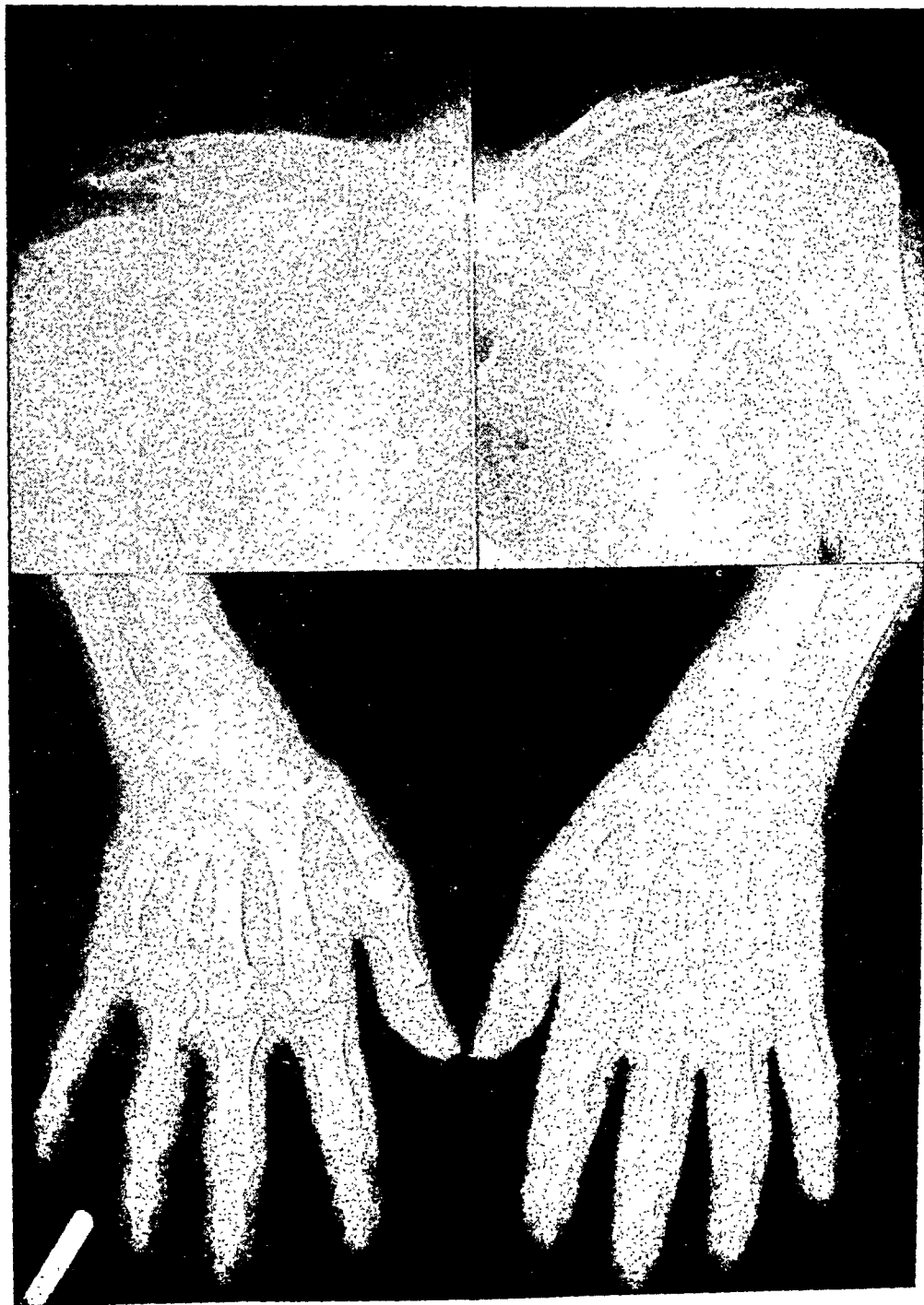


FIG. 2. Typical osteoporosis, wrist and small joints of patient in figure 1. Some decalcification of left humeral head.

in two instances. The color of the affected hand is apt to be a dusky pink or red at first. Later, the swollen tissues become pale or even cyanotic. Limited mobility at the finger joints is noticed. Attempts at passive motion at these articulations often induce pain. The patient usually holds the hand and fingers in a position of slight flexion. The grip is weak.

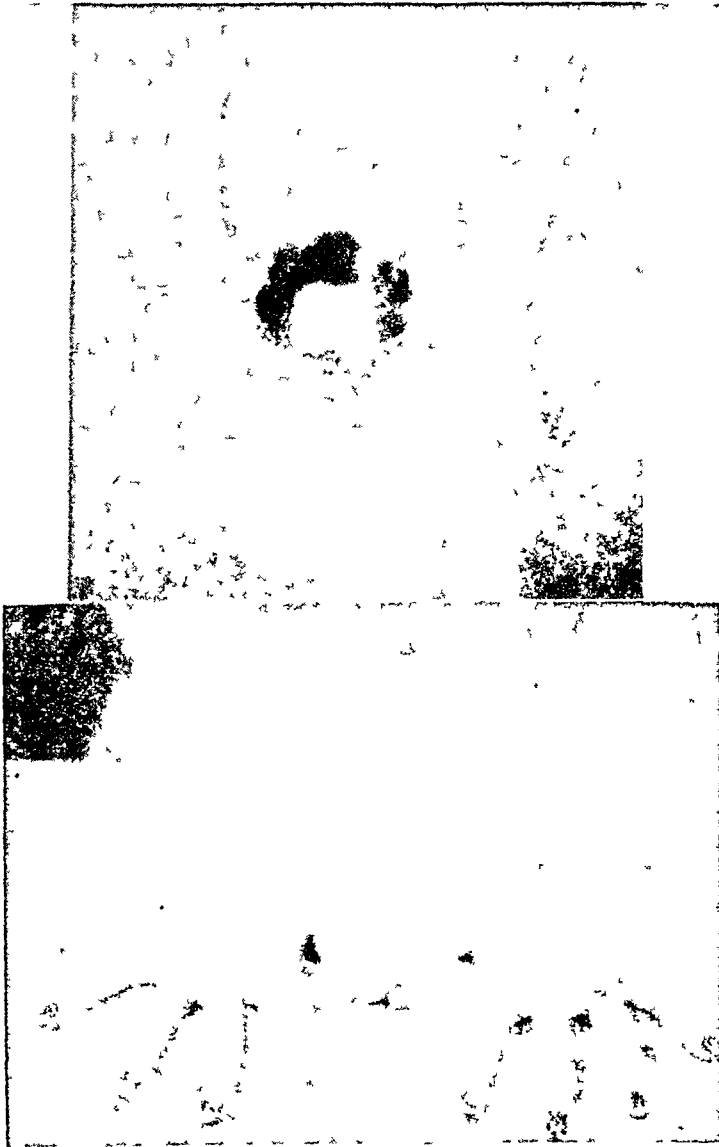


FIG. 3. Successful treatment; recovery about one year from onset (patient in figure 1).

The cutaneous temperature of the limb, especially of the hand, is elevated. The blood flow to the extremity, as reported in plethysmographic and oscillometric studies,<sup>5-8</sup> is likely to be increased. Venograms done by us have shown a suggestive but not, as yet, diagnostic pattern. Hyperreflexia may

be elicited in the affected extremity. At this stage roentgenograms of the hand usually exhibit slight, if any, osteoporosis, excepting in traumatic disorders when the decalcification, mottled or "ground-glass" appearance, of the wrist or even of the whole hand or extremity may develop with astonishing rapidity (figure 2).

The *second stage* (figure 4), which likewise is apt to last three to six months, is characterized by gradual relief of the painful shoulder dysfunction

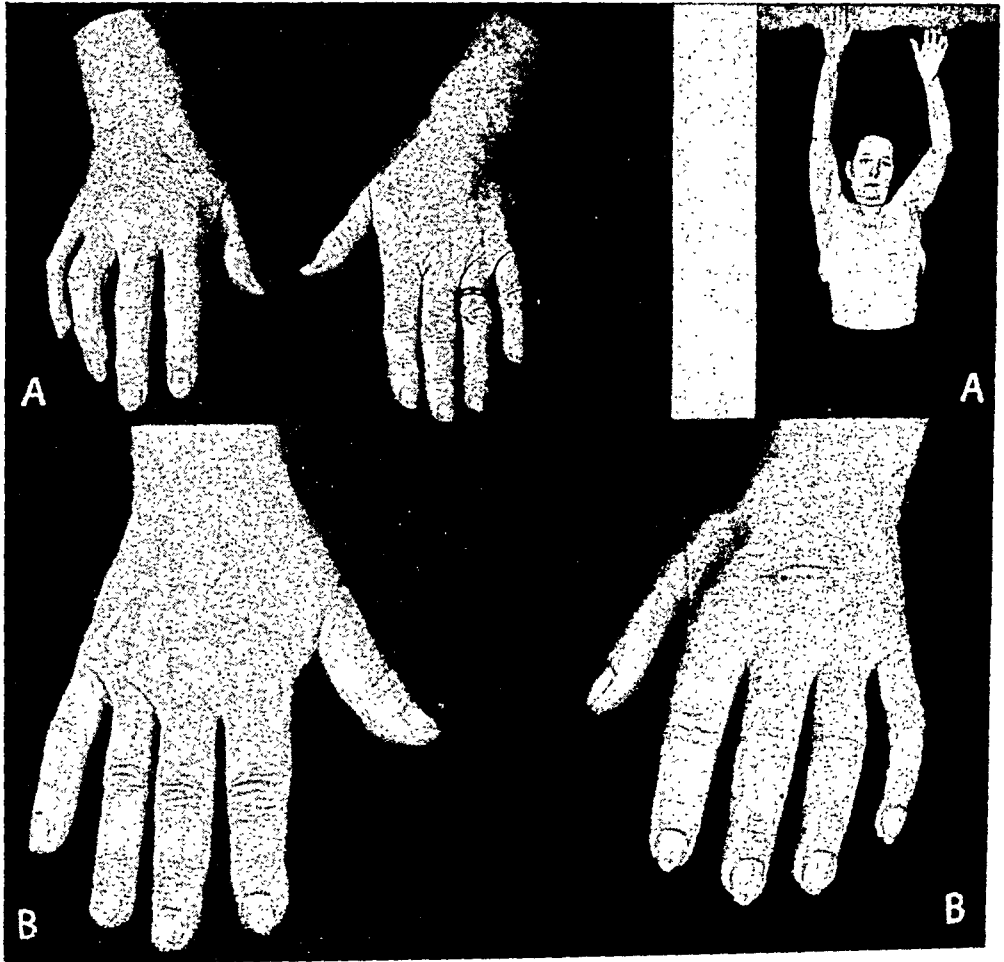


FIG. 4. Phase 2. In 4a residual disability at shoulder still present. Swelling of hand resolved in both cases; note smoothing of skin folds on dorsum of fingers; shiny, atrophic skin and digits; in 4b beginning flexion contracture more marked.

and resolution of the swelling of the hand. As the swelling subsides, the stiffness and flexion deformity of the fingers become more pronounced in cases with progression. Atrophy of the subcutaneous tissue and intrinsic muscles of the hand may now begin to become apparent. Rolling up of localized areas of the palmar fascia may be noticeable, or early signs of a Dupuytren-like contracture with or without its cutaneous callus may appear. Early trophic changes in the skin are observed for the first time. Reaction

of degeneration in the affected extremity was reported in some of his patients by Oppenheimer.<sup>37</sup> Patchy osteoporosis of the bones of the hand becomes more striking in the roentgen-ray films. The cutaneous temperature, previously elevated, begins to fall. The blood flow to the limb diminishes.<sup>5-8</sup>

The *third stage* (figures 5, 7), which lasts months or goes on to irreversible alterations, is characterized by the marked progression of trophic changes in the hand. The skin becomes smooth, glossy and drawn, with great diminution in the number of creases and wrinkles. Atrophy of the subcutaneous tissue advances. With the developing trophic alterations of the skin there is frequently seen a hypertrichosis, particularly noticeable on the dorsal surface of the fingers. The blood flow to the extremity is di-

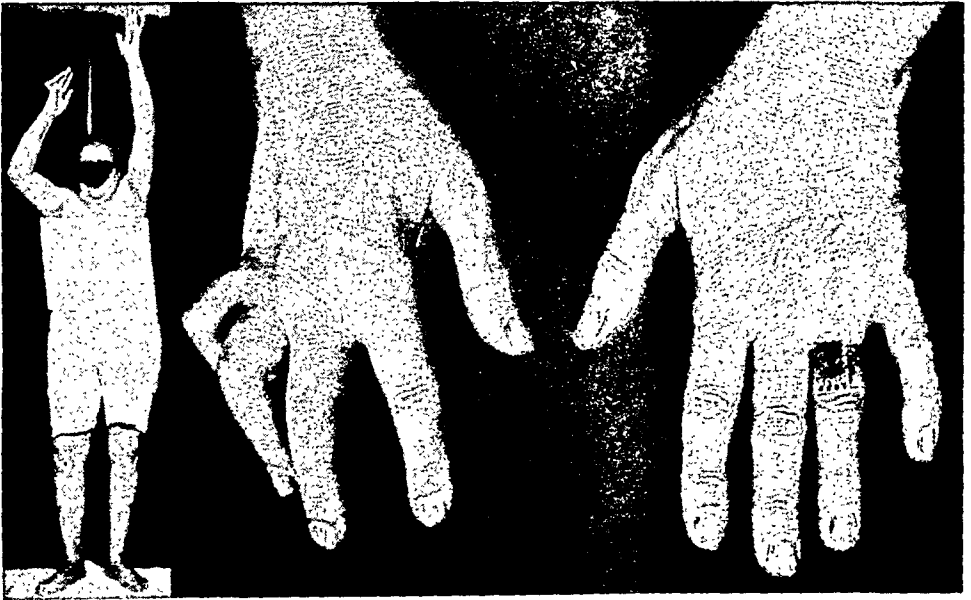


FIG. 5. Phase 3. Contractures with trophic changes of fingers; similar changes in the shoulder not common. Nine years after onset shown in figure 6d.

minished and the cutaneous temperature drops, especially over the hand and fingers. Oscillometric readings at the wrist may be lowered. The hand shows great atrophy of the interosseous muscles with severe limitation of motion at the metacarpophalangeal and interphalangeal joints. Contractures of the flexor tendons occur often at this stage, particularly on the ulnar side (figure 7). Subluxations are present occasionally. Rolling up of the palmar and digital fascia, in many ways like Dupuytren's contracture, is common. The roentgenograms at first show spotty decalcification of the small bones of the hand and of the metaphyses of the long bones. Osteoporosis of the humeral head often occurs when shoulder disability is prolonged (figure 2). Later this bone atrophy may become very widespread and diffuse.

## CLINICAL FORMS OF REFLEX DYSTROPHY OF THE UPPER EXTREMITY

It has been mentioned that in some cases reflex neurovascular dystrophy of the upper extremity, whether idiopathic or associated with any of the known provocative factors, is evidenced by isolated signs which usually enter into the complete clinical picture of the shoulder-hand syndrome. For example, some patients present only swelling, and finally atrophy, of the hand without shoulder disability; others exhibit painful disability of the shoulder as the sole manifestation; and still others may show contractures of the palmar fascia and/or flexor tendons without additional shoulder or hand

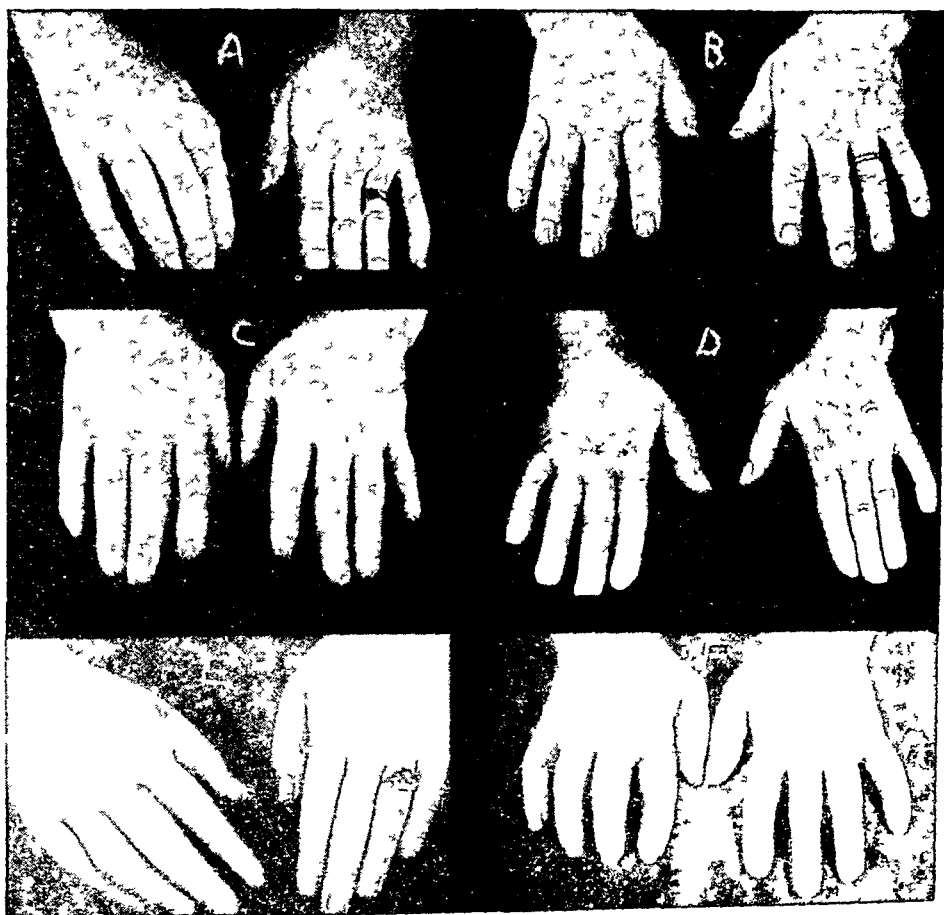


FIG. 6. Clinical similarity of early hand signs with varied causes: (a) Weber-Christian disease; (b) after herpes zoster of right arm; (c) after infectious arthritis of right middle finger, (d) idiopathic; (e) idiopathic; (f) probably post-traumatic.

symptoms. We have seen patients complaining of pain in the upper extremity whose only objective signs were tenderness with vasospasm or vasodilatation of the hand. It has been postulated<sup>38</sup> that some myalgias or fibrositis may represent a circumscribed neurovascular manifestation in the soft tissues. The clinical signs in many cases of rheumatoid arthritis suggest the influence of reflex neurovascular factors.

In many subjects some of these limited features of reflex dystrophy occur as musculoskeletal symptoms without any visceral disease, and cannot be shown to arise as a reflex neurovascular disturbance. Without other characteristic signs or some acceptable precipitating factor, it obviously would be difficult and probably incorrect to classify such instances as reflex dystrophic disorders in the present state of our knowledge. Painful shoulder disability is the most common example.

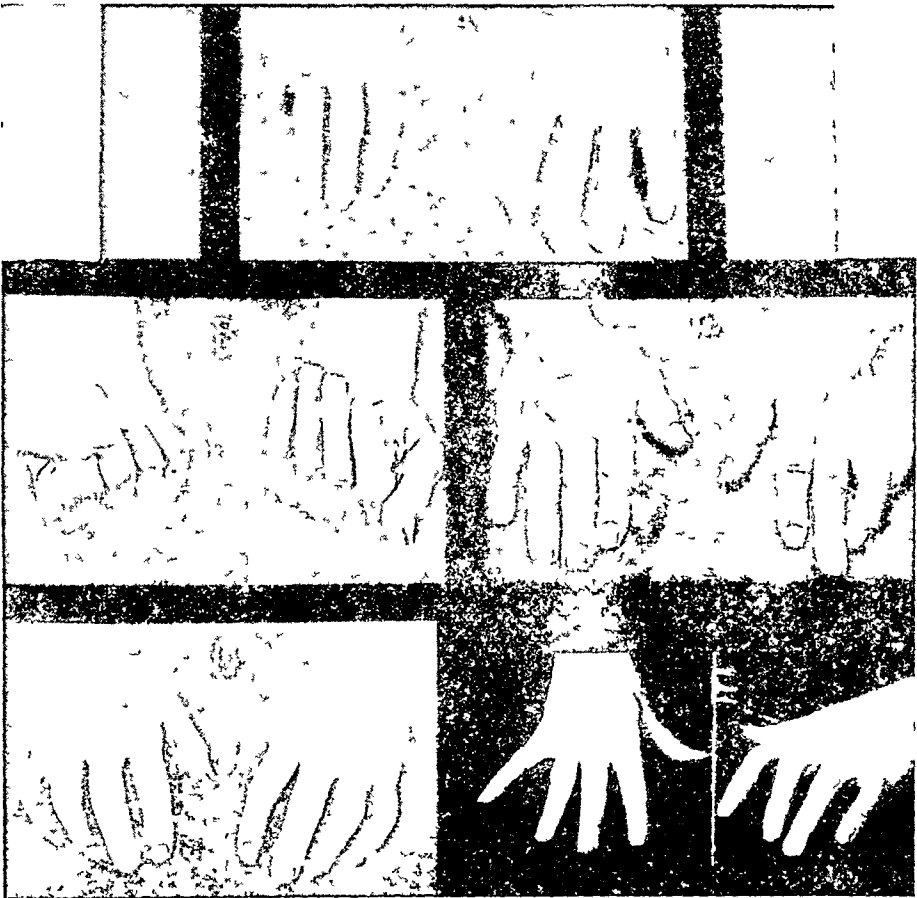


FIG 7. Clinical similarity of terminal (permanent?) disabling hand signs in (a) post-hemiplegic (2 yrs.), (b) post-infarctional (9 yrs.), (c) idiopathic (3 yrs.), (d) post-infarctional, bilateral ( $1\frac{1}{2}$  yrs.), (e) idiopathic (5 yrs.)

Ordinarily, however, the limited manifestations of reflex dystrophy can be distinguished and should be regarded then as incomplete forms of the condition. The partial as well as the more complete symptom-pictures may be due to various causes (table 2). de Takats has described a classification based on the neurone level involved.<sup>9</sup> The etiologic varieties of reflex dystrophy found in our cases are listed in table 3. A number of other underlying diseases not tabulated have been mentioned in the literature—polio-myelitis, syringomyelia, pulmonary infarction and tumors of the cord and

brain. Undoubtedly many additional primary disorders ultimately will be recognized as the source, when a search is made regularly for dystrophic complications.

In two patients observed, but not included in this series, neoplasms in the supraclavicular area produced the shoulder-hand syndrome either as a reflex

TABLE III  
Reflex Dystrophy of the Upper Extremity  
Etiology in 42 Cases

Idiopathic	11
After myocardial infarction	9
Post-traumatic	5
Post-hemiplegic	5
Post-herpetic	2
Diffuse vasculitis	2
Cervical osteoarthritis	2
Panniculitis	1
Gonococcal arthritis	1
Multiple or inconclusive	4

N.B. 36 cases presented the shoulder-hand syndrome; 6 cases showed only painful swelling and atrophy of hand.

(Some of these cases studied by courtesy of Drs. Russell Cecil, Richard Freyberg, Stewart Gillmor, John Gray, Herman Tillis and C. H. Traeger.)

reaction to infiltration of nerves or ganglia or from compression of sympathetic neural elements. Occlusion of large blood vessels by the enlarging new growth soon adds to the complex clinical picture in such cases. In the early stages of symptoms in these patients, compression of fibers entering or leaving the ganglia, or of ganglionic tissue, produced the picture of sympathetic stimulation, as well as shoulder disability, postulated in reflex dystrophy. These patients practically provide an *in vivo* reproduction and proof of the mechanism which has been deduced from clinical observation.

#### INCOMPLETE FORMS OF REFLEX DYSTROPHY OF THE UPPER EXTREMITY

*Painful Vasodilatation and Vasoconstriction.* Disturbances of the upper extremity characterized by localized painful vasodilatation or vasoconstriction sometimes may constitute incomplete or abortive forms of reflex dystrophy, or they may be the forerunners of more extensive reflex disorders gradually developing. We have observed these symptoms shortly after traumatic lesions and cerebrovascular accidents. A fairly high incidence has been noted recently in poliomyelitis.<sup>39</sup> It is possible that in some disorders of the upper extremity, particularly certain cases designated as scalenus anticus syndrome or as the costoclavicular syndrome, in which pain and vasomotor changes are the outstanding features, a form of reflex dystrophy actually is present. Hyperhidrosis has been an infrequent and minor symptom in our patients.

*Contractures of the Palmar Fascia and Dupuytren's Contracture.* Dupuytren's contracture<sup>21-26</sup> usually behaves like a benign fibroplasia of the

palmar connective tissue. It may occur in primary form or in association with various diseases. It has been reported as a common sequel to myocardial infarction with or without associated shoulder and hand symptoms.<sup>18-20</sup> For example, contractures of the palmar fascia, in many ways like Dupuytren's, have been found by Askey<sup>19</sup> in seven of 10 cases of post-infarctional shoulder and hand disabilities. Kehl<sup>40</sup> in 1943 reported six cases following coronary occlusion, five of which were associated with shoulder and/or hand symptoms. In the same year Alf Johnson<sup>20</sup> described palmar contractures in 23 of 39 cases of what he termed "post-infarctional sclerodactylia."

Contractures of the palmar fascia and of the flexor tendons in many respects similar to Dupuytren's are common findings in the shoulder-hand syndrome. They also occur in our experience as simple, isolated, uncomplicated features in some cases, as well as in patients with cardiac or pulmonary disease. These palmar changes have been noted by us much more frequently since we have begun to look for them.

The origin of the fascial contractures in the palm is unknown, but they have been considered by some observers, notably Nippert<sup>25</sup> and Powers,<sup>26</sup> to be the result of a disturbance of the sympathetic innervation. Powers<sup>26</sup> states that Dupuytren's contracture is "not an isolated condition nor a clinical entity, but usually an effect of past or present visceral disease." It is related, in his opinion, to scleroderma, hypertrophic pulmonary osteoarthropathy, Raynaud's disease, and other trophic disorders often occurring together. The palmar changes are attributed by him to the irritation and hyperexcitability of the sympathetic nervous system aroused by the underlying visceral disease.

*Swelling and Atrophy of the Hand.* Swelling and atrophy of the hand unassociated with shoulder disability, with or without palmar contracture, has been observed by us as a sequel to hemiplegia, herpes zoster and trauma to the upper extremity. We have seen this disorder in two patients whose only associated abnormality was cervical osteoarthritis with narrowing of the vertebral foramina by hypertrophic changes. In all of these patients, the temperature changes, pain and trophic features at the hand were consistent with a limited form of reflex neurovascular dystrophy. In our series of 42 cases of reflex dystrophy in the upper extremity, six presented only swelling and/or atrophy of the hand without shoulder involvement.

*Painful Disability of the Shoulder.* Painful disability of the shoulder as the sole manifestation of reflex dystrophy appears to be a not uncommon aftermath of coronary artery occlusion and hemiplegia. It has also been seen by us in patients with Parkinsonism and after a variety of disabling intrathoracic diseases in elderly people.

#### THE COMPLETE FORM OF REFLEX DYSTROPHY OF THE UPPER EXTREMITY

*The Shoulder-Hand Syndrome.* The usual characteristics of the clinically complete form of reflex dystrophy of the upper extremity, the shoulder-



hand syndrome, have already been described. Like the incomplete forms, it may be due to a number of causes enumerated in table 3. Although the signs are comparatively similar in the shoulder-hand syndrome regardless of the basis, some aspects of the clinical picture in each etiologic variety are worthy of comment. Because some of these entities have received little or no attention in the literature, at least recently, a more detailed discussion of their background and distinctive features will be presented.

We refer to the "clinically complete" form of reflex dystrophy when the shoulder and hand are affected, because it represents the most extensive reflex symptom-complex ordinarily seen. We have encountered only two patients with the shoulder-hand syndrome presenting symptoms at the elbow joint. For some reason, not clear at present, this articulation and its connected structures usually escape involvement. The use of the term "shoulder-hand syndrome," then, is intended to imply a reflex neurovascular disturbance of which shoulder involvement is an important sign. Somehow this feature seems to have gone unrecognized as a further manifestation of the reflex mechanism even in the latest publications.

In several of our patients the shoulder symptoms had resolved when they finally sought relief of the hand complaints. The complete evolution of the clinical picture then would have been missed without a thorough history.

The classic concept of reflex neurovascular dystrophy following some form of external violence has been established so firmly by Sudeck's description of post-traumatic osteoporosis that a history of trauma has come to be expected or assumed when trophic symptoms are encountered in an extremity. In medical conditions complicated by reflex dystrophy we are actually confronted with internal irritation or injury as the precipitating factor. It must be concluded, therefore, that the similar clinical pictures seen with the varied etiologic considered here may be produced by either internal or external tissue trauma acting through an identical neurophysiologic mechanism to be discussed later.

#### ETIOLOGIC VARIETIES OF COMPLETE REFLEX DYSTROPHY OF THE UPPER EXTREMITY

*The Idiopathic Shoulder-Hand Syndrome.* The idiopathic variety, which we wish to emphasize especially, has exhibited the shoulder-hand syndrome in its complete form in all of our cases so far. No etiologic factor has been found in any of the 11 patients who comprise this group, nor has there been any history of injury. Undoubtedly in many such instances the signs have gone unrecognized in the past or have been assumed to follow some minor trauma to the extremity even when the patient could not recall any. In other cases the most striking symptoms were attributed to acute bursitis, periarthrits, scalenus anticus syndrome, atypical rheumatoid arthritis, non-specific infectious arthritis, gout or scleroderma, according to the stage of the disorder.

As a result of Sudeck's original description of the neurovascular syndrome due to suppuration or external trauma, even in the definite absence of a history of injury, an unnoticed or forgotten sprain or torsion is more apt to be taken for granted as the etiologic factor in many patients with merely "spontaneous" complaints. For example, "spontaneous" symptoms of unknown etiology have been mentioned by Noble and Hauser<sup>4</sup> as occurring in 12 of the 48 cases of acute bone atrophy reported by them. Undoubtedly these would fall into our idiopathic group. So long as a definite, provocative factor is not demonstrable, it is probably desirable to keep these patients segregated as presenting a distinct "idiopathic" entity.<sup>33a</sup> Some definite physiologic abnormality or incipient pathology underlying this clinical picture, so far unrecognized, may be established in future. Studies on costoclavicular and neurovascular disorders of the shoulder arising from mechanical, vascular and developmental defects at the thoracic inlet in time may explain some of these idiopathic cases.<sup>42-44</sup> Until a fund of information acquired by postmortem and surgical exploration of more of these subjects with "spontaneous" symptoms accumulates, as in the recent study of Telford, our information must remain inadequate to explain the cause of the idiopathic disorder and its basis must be considered unsettled.

#### THE SHOULDER-HAND SYNDROME, POST-TRAUMATIC

*Causalgia.* This condition and its relation to Sudeck's atrophy and other forms of reflex dystrophy have been discussed extensively by de Takats,<sup>5-8</sup> Livingston,<sup>2</sup> and others.<sup>34, 35</sup> It was first described by Weir Mitchell,<sup>1</sup> occurring as an occasional sequel to injury of a peripheral nerve (most commonly the median nerve), characterized by the following symptoms: (1) the presence of severe, constant, throbbing or burning pain in the affected limb; (2) exquisite cutaneous hyperesthesia with extreme hypersensitivity to the environment, so severe that the lightest stimulus or emotion will induce agonizing paroxysms of pain; (3) extensive trophic changes, especially glossy skin; and (4) variable cutaneous temperature and other vasomotor disturbances. The impression is inescapable in these cases that there often exists a superimposed psychogenic factor as well. Causalgia, therefore, is a form of reflex dystrophy occurring in association with injury to a peripheral nerve, in which burning pain and hypersensitivity to stimuli are the outstanding features. One patient in our series could be classified in this category.

Minor causalgia is a term coined by Homans<sup>3</sup> to describe a form of reflex dystrophy in which pain is a less conspicuous feature than in true causalgia, but in which the symptomatology is otherwise similar.

#### POST-TRAUMATIC OSTEOPOROSIS (SUDECK'S ATROPHY)

The bone atrophy which bears his name was first established as a definite clinical entity by Sudeck<sup>9</sup> in 1900. In 1877 and in 1883, Wolff<sup>45, 46</sup> had

described the occurrence of trophic changes in the limbs of patients following infection or resection of a joint. He then originated the theory of an underlying trophoneurosis. In 1895 Kümmell<sup>47</sup> reported six cases of bone atrophy following slight trauma. Additional papers by Sudeck<sup>10, 11</sup> and Kienböck<sup>48</sup> appeared in 1902. They further clarified the clinical picture and gave accurate roentgenologic descriptions of the bony changes. They showed clearly that inactivity alone could not account for the degree of bone atrophy observed, that it appeared long before the atrophy of disuse, and even occurred in certain cases while the limb was in use. Originally Sudeck felt that the condition was inflammatory in origin but later subscribed to Kienböck's view that it was a trophoneurosis. Sudeck's atrophy subsequently received considerable attention from German authors, and to a lesser extent from the French, especially Leriche<sup>49</sup> and his co-workers. Noble and Hauser's paper<sup>4</sup> in 1926 was the first reference to this subject in the English and American literature. Since then many reports have appeared, notably those of Fontaine and Hermann,<sup>50</sup> Gurd,<sup>51</sup> Hermann and Caldwell,<sup>52, 53</sup> de Takats and Miller,<sup>5-8</sup> and Sweetapple.<sup>41</sup>

Sudeck's atrophy, otherwise known as post-traumatic osteoporosis, acute bone atrophy, peripheral trophoneurosis, etc., when it involves the upper extremity, is undoubtedly a form of reflex dystrophy. It may affect the upper or lower extremity. It occurs also in the spine.<sup>4</sup> The condition has been reported after minor fracture, injury or sprain, often about the wrist or ankle joint. Generally, the first clue to its recognition is the appearance of severe, constant throbbing or burning pain with paroxysmal exacerbations, in a patient whose injured limb, to all appearances, is properly immobilized, uninfected and healing satisfactorily. Placing the part in a cast or support aggravates the pain. The onset usually occurs within two weeks of the time of injury. More rarely it follows a suppurative lesion of the limb. The pain then ushers in the train of symptoms and signs already described as characteristic of reflex dystrophy. Sudeck's atrophy of the upper extremity represents a variety of the shoulder-hand syndrome, due to trauma or supuration, when clinically complete signs arise. Incomplete reflex symptoms are common here.

#### THE SHOULDER-HAND SYNDROME, POST-(MYOCARDIAL) INFARCTION

For some years clinicians have been aware of the occurrence of persistent painful shoulder disability following coronary occlusion.<sup>1</sup> Almost 50 years ago Osler mentioned the "motor disability" at the shoulder observed by him in some patients after "anginal attacks."<sup>13a</sup> In 1930 Howard reported five cases illustrating the presence of a stiff, painful shoulder simultaneously with, or following, severe myocardial disease. He emphasized the importance of recognizing this association for two reasons: (1) the pain of "periarthrititis" of the shoulder might be mistaken for severe cardiac pain, or (2) the shoulder lesion might receive attention while the changes in the heart are overlooked. The shoulder disability was regarded by him as

basically a "periarthrititis" resulting from referred pain with attendant partial immobilization, loss of tone, mechanical maladjustments, and secondary inflammatory changes. He thought that this combination of shoulder dysfunction and cardiac disorder was so frequently encountered that a causal relationship was suggested.

Libman<sup>14</sup> likewise noted the frequent co-existence of shoulder pain and angina pectoris. It was his opinion that they were both caused by the same metabolic disorder. He pointed out that a "subacromial bursitis" will not infrequently begin shortly after a coronary thrombosis has occurred.

In 1936 Edeiken and Wolferth<sup>15</sup> reported 14 cases with persistent shoulder pain following myocardial infarction, appearing coincidentally up to 16 weeks following the heart attack, and lasting weeks to years. They found the condition unilateral or bilateral, most frequently the former. The cardiac lesion was considered by them to be an important etiologic factor. It was their impression that the incidence of this symptom among survivors from infarction might exceed 10 per cent. To them the symptomatology suggested "an analogy to causalgia." They found neither local nor roentgen-ray therapy of any value in treatment.

Boas and Levy<sup>16</sup> in 1937, and Leech<sup>17</sup> in 1938, also reported observing a painful stiff shoulder in patients with coronary artery disease. Boas and Levy postulated two possible mechanisms for the shoulder disorder: first that radiation of the anginal pain to a shoulder already the site of slight pain might, by summation, produce the painful disability: and second, that the afferent pain impulses from the heart might sensitize neurons whose fibers enter into the brachial plexus.

Ernstene and Kinell noted the occurrence of persistent pain in one or both shoulders as a relatively common sequel to myocardial infarction.<sup>18</sup> They found 17 cases of persistent pain in the shoulder region in a series of 133 consecutive cases of myocardial infarction. In six of their 17 cases symptoms of "rheumatoid arthritis" involving the hand joints developed simultaneously with, or subsequent to, the shoulder symptoms. The "remarks" for two of their cases indicate that the authors had observed changes in the hand and fingers not unlike those described for reflex dystrophy. They did not, however, relate the hand changes to the shoulder disability. It is interesting to note here Osler's reference in 1897 to Eichhorst's observation that some of his patients had presented "atrophy of the muscles of the hand" after anginal attacks.<sup>13a</sup> Recently ulcerative lesions of the digits after myocardial infarction have been reported.<sup>13c</sup>

Askey regarded the combination of hand and shoulder symptoms following infarction as a definite syndrome.<sup>19</sup> He reported 22 cases illustrating the combined symptoms and clearly described the shoulder disability and hand changes that are the subject of this paper. He found Dupuytren's contracture in seven of 10 cases examined for this particular condition. Askey looked upon the hand involvement as an extension of the shoulder disability previously described by others. He believed that the syndrome is

related to myocardial infarction and is caused by a "combination of sympathetic disturbance and arthritis, with varying degrees of preponderance of one or the other." He was careful to state, however, that "the course of the hand disability was characteristic of neither long-standing rheumatoid arthritis nor osteoarthritis."

In 1943 Johnson reported a series of 39 patients, of 178 consecutive cases of myocardial infarction, who exhibited trophic changes in the hand resembling "sclerodactylia." Thirty-four of these also showed unilateral or bilateral shoulder pain and disability. He accurately described the hand changes which he believed to be analogous to those occurring in Raynaud's disease and scleroderma. Hence he suggested for them the name of "post-infarctional sclerodactylia." He did not consider the shoulder symptoms to be related to the hand changes or to be of the same etiology. They were regarded by him as the result of voluntary or involuntary splinting of the joint. The hand changes, he thought, were due chiefly to ischemia of reflex origin, augmented by local anoxemia due to arteriosclerosis and systemic anoxemia of cardiac origin.

The clinical pattern of the post-infarctional type of shoulder-hand syndrome resembles that due to other causes. Typically, the dystrophic process has its onset three to 16 weeks after acute myocardial infarction or following long-standing angina pectoris. The shoulder disability generally, but not invariably, precedes the changes in the hand by an interval of a few weeks. Usually, the symptoms are bilateral but unilateral localization at either the right or left upper extremity is not uncommon. The question of whether the side of radiation of the cardiac pain predisposes to the subsequent localization of the syndrome is at present unsettled by the conflicting reports in the literature on this point. The occurrence or localization of the symptoms bears no relationship to the site of myocardial infarction. They appear following both anterior and posterior wall involvement. The additional development in some of these cases of contractures of the palmar fascia and of typical Dupuytren's contracture has already been discussed.

This etiologic variety of the shoulder-hand syndrome has been found by us most frequently to run a stubborn course. Most of our cases were seen, however, in the later stages.

#### THE SHOULDER-HAND SYNDROME, POST-HEMIPLEGIC

Ever since Chevallier's report in 1867, it has been recognized that vasomotor changes are often present in extremities paralyzed by cerebral lesions. From a brief survey of the literature on hemiplegia for symptoms characterizing reflex dystrophy it is apparent that many of the features which are typical of this complication have been observed in the paretic limbs of some hemiplegics.<sup>28-32</sup> The changes recorded include particularly swelling, changes in skin temperature, vasomotor disturbances, and, in rare instances, trophic changes. "Arthritic changes, especially in the shoulder"<sup>34</sup> have

also been noted as an interpretation of the unusual stiffness and limited mobility which may develop. Yet in none of the reports of these observations have they been recognized as a form of reflex dystrophy. The only references to this point in the literature to our knowledge, are statements by de Takats<sup>8</sup> and Evans<sup>34, 35</sup> that causalgic states may follow cerebral lesions. de Takats<sup>8</sup> mentions one case of cerebral thrombosis and Evans<sup>34, 35</sup> lists one of a thalamic syndrome, each of which was followed by reflex dystrophy.

In hemiplegia the vascular lesion which destroys the motor functions, undoubtedly, likewise interferes with the control of the autonomic nervous system normally exerted by the higher centers. In that way it may predispose to the subsequent development of the shoulder-hand syndrome. Indeed, the paretic limb frequently presents the symptoms of a mild form of reflex dystrophy which in most cases undergoes spontaneous resolution. In some instances, however, far more often than has been recognized, the changes are progressive and the florid picture of reflex dystrophy of the upper extremity develops. We have observed four individuals with the post-hemiplegic shoulder-hand syndrome within a short period. Reflex changes may occur in the lower extremity. Oddly enough, shoulder disability is a less prominent characteristic of this variety of reflex dystrophy, probably due to masking by the paralysis. Furthermore, in two of these patients we have found pain, tenderness and limitation of motion at the elbow. Symptoms at this joint have not been observed by us so far in any of the other etiologic varieties of reflex dystrophy. The remaining features presented by these subjects follow the pattern already described.

#### THE SHOULDER-HAND SYNDROME, POST-HERPETIC

In 1938, Marques reported a case of osteoporosis following an attack of herpes zoster brachialis. He pointed out the rarity of the observation. His patient presented the usual symptoms of the dystrophic process with roentgenologic changes in the hand "characteristic of Sudeck's atrophy." He noted the similarity to post-traumatic osteoporosis as described by Leriche, Fontaine and their co-workers. The only other reference to this condition in the literature that we have been able to find is a statement by de Takats<sup>8</sup> that herpes zoster may be complicated by reflex dystrophy. We have observed two patients in whom neurovascular dystrophy has followed, by three and six weeks respectively, an attack of herpes zoster of the now affected upper extremity. Their symptoms were typical for the hand involvement, although they recall no shoulder disability.

#### THE SHOULDER-HAND SYNDROME, SECONDARY TO CERVICAL OSTEOARTHRITIS

In 1938 Oppenheimer<sup>37</sup> reported a series of 14 patients with swelling and atrophy of the hand associated with radiologic evidence of intraforaminal

constriction at one or more of the upper four cervical vertebrae. The encroachment on the interspaces he found to be secondary to one of the following: degenerative disc disease with, or without, intraforaminal exostoses; previous compression fractures or subluxations of the vertebrae; or simple reduction of the intervertebral lumen by osteoarthritic spurs.

All of the patients had been troubled with recurrent "rheumatic pains" in the shoulder region of the affected side, and by paresthesias in the fingers for periods of several weeks to 20 years. Oppenheimer apparently did not relate this shoulder pain to the condition of the hand, nor did he mention tenderness or any limitation of function at the shoulder. Six of the cases showed osteoporosis of the hand. He concluded that of seven patients treated with ultra-short wave diathermy to the cervical spine, he effected a remission of symptoms in six. He did not correlate the condition described by him with any other disorder, nor did he elucidate the basis for the development of atrophic swelling of the hand from the cervical osteoarthritis seen in his roentgen-ray films.

It is clear from the foregoing discussion that the disorder described by Oppenheimer represents a limited form of reflex dystrophy attributed by him to intraforaminal constriction in the cervical spine of osteoarthritic, discogenetic or traumatic origin. Although our patients, so far, have represented largely the older age groups, the absence of any demonstrable abnormality in the cervical spines of many of these cases reasonably excludes osteoarthritic pathology as a uniform predisposing factor in the shoulder-hand syndrome, if at all. One of our patients, a 15 year old female, showed the normal cervical spine to be expected at that age.

#### THE SHOULDER-HAND SYNDROME, SECONDARY TO VASCULITIS

The systemic angiopathies such as periarteritis nodosa and diffuse arteritis, as a result of lesions in the periphery or possibly in the spinal cord and ganglia, or even localized thrombophlebitis, may provoke classic reflex dystrophy as a complication. We have studied two such cases with diffuse arteritis and Evans has reported one.

#### THE SHOULDER-HAND SYNDROME, SECONDARY TO NODULAR PANNICULITIS

We have observed one patient with febrile, relapsing, non-suppurative, nodular panniculitis (Weber-Christian) complicated by neurovascular dystrophy. The only pannicular invasion of the upper extremities had consisted of a solitary nodule in the deltoid area on the dystrophic side. This lesion was followed in a few weeks by insidious development of the shoulder-hand syndrome which had persisted about five months after the bout of nodular panniculitis had resolved. To our knowledge this is the only instance of reflex dystrophy as a complication of Weber-Christian disease.

## MECHANISM OF THE SHOULDER-HAND SYNDROME

Studies on the dynamics of this disorder have concerned largely the traumatic cases. These have consisted of attempts to explain the obvious vasomotor changes and the distinctive types of pain seen in the post-traumatic syndrome. The peripheral, injured area has been accepted as the site of origin of afferent stimuli with the sympathetic system as the efferent branch of the reflex.<sup>2, 5, 34, 35, 49, 50</sup>

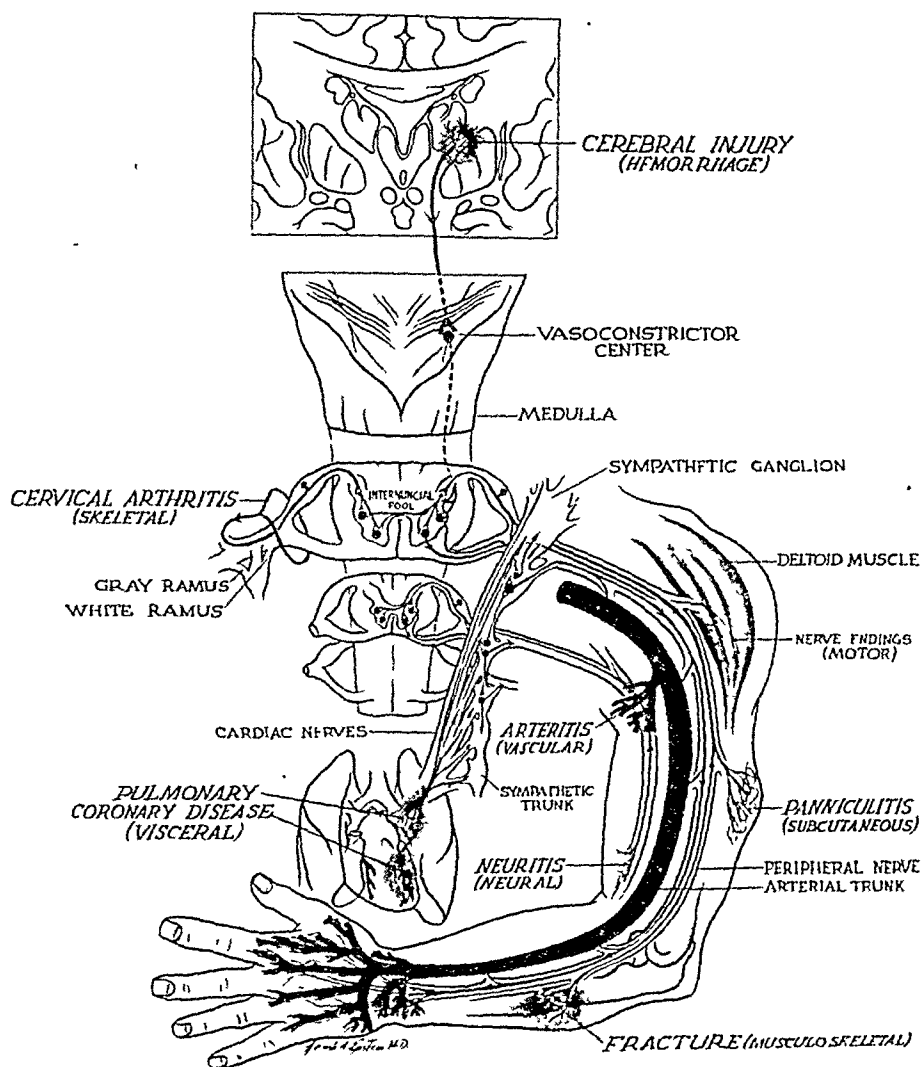
According to the rapidly growing impression, external trauma constitutes only one source of reflex dystrophy. As we have stated, the syndrome arises from many different causes. A more inclusive physiologic clarification, therefore, is in order. It must take into account these pertinent clinical facts: (1) conditions of widely separated location, such as myocardial infarction, herpes zoster, peripheral injuries, etc., can cause practically the same clinical picture; (2) this disorder seems to involve not only the autonomic system, parasympathetic as well as sympathetic, but also the motor pathways to muscles; (3) the disturbance does not show a definitely segmental distribution; and (4) it is often improved or abolished by interruption of the sympathetic nerve supply to the upper extremity.

Any working explanation of the reflex mechanism must remain hypothetical to a great extent, since it must depend on some of the current concepts in neurophysiology which cannot be verified by clinical methods to the exclusion of all the others. An abundant literature supports the idea of an axone reflex and/or of antidromal stimulation from a focus of irritation or injury. However, the probable rôle in this syndrome of the internuncial pool, as developed by Lorente de Nó<sup>55</sup> and elaborated by Livingston,<sup>2</sup> appears to offer the clearest understanding of its dynamics. The clinical picture seen in the shoulder-hand syndrome embraces a medley of signs and symptoms which must be effected through the autonomic, more noticeably the sympathetic, and cerebrospinal outflows of several cervical and thoracic spinal segments. The afferent stimuli may be assumed to arise in a general way from a focus of physiologic irritation or from a local, injured area in the extremity, the heart, the cortex, etc.—any site of external or internal disturbance or violence to tissue (figure 8).

In many cases, as for example in cerebral lesions, the afferent stimuli must enter cord segments far removed from those supplying the upper extremity. Owing to this fact and to the rather diffuse nature of the signs in the shoulder-hand syndrome, the segments involved usually defy accurate neurologic localization. The mechanism can be readily conceived, however, as a widespread disturbance of the internuncial pool. Recent neurophysiologic investigation<sup>55</sup> shows this pool to be an extensive network of interconnecting neurones in the central gray matter, extending over many segments. At these levels potential connecting pathways are formed between incoming impulses and motor neurones of either the sympathetic (posterolateral) or anterior horn cells.



The internuncial disturbance may be visualized as arising in this manner: Following a myocardial infarction, for example, afferent stimuli traverse the cardiac nerves to enter the cord at levels  $T_1$ - $T_4$ . These new and profound stimuli strongly activate the internuncial pool in that area of the cord. The



### Mechanism Of The Shoulder-Hand Syndrome (Reflex Dystrophy Of The Upper Extremity) *after de No and Livingston*

FIG. 8. A diagrammatic representation of current neurophysiologic concepts applied to the shoulder-hand syndrome and some of its causes.

disturbance spreads upward with effects on the anterior horn cells, causing disability of the shoulder muscles. It travels downward to involve the sympathetic neurones of the lateral horn cells innervating the upper extremity. The continuous activity of the internuncial pool and the chronicity

of the shoulder-hand condition may be due to self-exciting, and self-perpetuating, closed chains established at various points in irregular fashion, as described by Lorente de Nó. The severity of the symptoms would depend on the intensity of the stimuli and rate of discharge of the chains of irritation. This diffuse involvement upward and downward of spinal cord segments would account for the fact that specific myotomes and dermatomes do not seem to be selectively affected in this syndrome rather than a good part of the upper extremity as we find.

The next consideration in discussing the mechanism of reflex dystrophy must be the beneficial results obtained from local interruption of the sympathetic system. Many of the clinical features clearly point to a neurovascular imbalance, predominantly of the vasomotor system. In the first stage of the disturbance, as already described, the hands are apt to be warm and swollen. This elevated surface temperature ordinarily is acknowledged to indicate an increased blood flow. Confirmatory evidence of this principle has been advanced by de Takats<sup>5,7</sup> in his observations on post-traumatic dystrophy. He reported that oscillographic pulsations are augmented. At the same time plethysmographic records show an increased blood flow in the affected extremity. Ellis and Weiss<sup>32</sup> studied hemiplegias complicated by the features regarded by us as the shoulder-hand syndrome. They found in most of them, by measurement of arterio-venous differences, that the blood flow was increased on the dystrophic side.

In the later stages of the syndrome a different type of vasomotor disturbance is present. The hand is generally cold. The skin appears thin and atrophic. Ischemia completes the evidence of vasoconstriction. Leriche,<sup>49</sup> who has written extensively on the subject, believes that trauma produces an instability of the autonomic nervous system which may lead to alternating and intermittent stages of vasoconstriction and vasodilatation. Either of these vascular phenomena, in his opinion, may persist as a chronic disorder.

In the later stages of the shoulder-hand syndrome, with the onset of trophic changes and diminished temperatures, the reason for the benefit from sympathetic block is fairly obvious. As a matter of fact, however, best results are obtained in the first phase, when the hand is warm and already shows evidence of an increased blood flow. The use of nerve block here seems paradoxical. Miller and de Takats<sup>5</sup> found that after sympathetic block the already augmented blood flow on the dystrophic side was further increased. These aspects of the underlying physiologic mechanism require further clarification.

The osteoporosis, which may develop early, probably represents an initial result of the hyperemia found in the early phase. It has long been known that bone atrophy follows any prolonged, deep hyperemia. It is unlikely that the decalcification found in this condition arises merely as a disuse atrophy. It has been demonstrated that disuse atrophy is a general decal-

cification that takes a much longer time to appear than the short interval peculiar to the disorder under discussion.<sup>10, 11, 48, 50</sup> Moreover, the osteoporosis of reflex dystrophy, as we have stated, is observed to develop in limbs that are functioning.

The pain of the shoulder-hand syndrome, particularly in the post-traumatic varieties, is attributed to stimulation of regular pain afferents in the vicinity of the traumatized or damaged area. It must be recalled, however, that an autonomic disturbance appears to be part of the "vicious circle" which maintains a state of irritability at the termination of the pain receptors, possibly by altering local metabolites, in that way leading to continuous stimulation or "bombardment" of the internuncial pool of the spinal cord.<sup>2, 49, 55</sup> When the efferent elements of this circuit, especially the sympathetic fibers, are interrupted, the "vicious circle" is broken and its attendant pain abolished. The relief of disability and muscle spasm following sympathetic block in these cases may be explained on the same basis. Despite the paradoxical features, difficult to clarify entirely in the present state of our knowledge, the fact remains that, empirically, interruption of the sympathetic nerve supply to the limb relieves pain, resolves the signs and restores function in the majority of cases with impressive rapidity.

#### THE DIFFERENTIAL DIAGNOSIS OF THE SHOULDER-HAND SYNDROME

It is important for many reasons to distinguish all forms of reflex dystrophy of the upper extremity from the many conditions they may resemble. Because the reflex signs in the limb may happen to be those first noticed, before the confirmatory evidence of disease in the thoracic viscera, brain, cord or regional musculoskeletal structures, their early, correct interpretation assumes great diagnostic importance. From a therapeutic standpoint the effective, early use of proper measures and the avoidance of strenuous treatment, employed in the diseases with which reflex dystrophy may be confused, make differential diagnosis an especially imperative consideration here.

The limitations of space permit us to discuss only the differential diagnosis of the complete form of reflex dystrophy, the shoulder-hand syndrome. The early stages of reflex shoulder involvement, particularly when acute and subacute, resemble bursitis and periarthritides (periarticular fibrositis). The local signs—pain (sudden or insidious), diffuse tenderness and disability in all ranges of motion—are similar to those seen in the uncomplicated peripheral disorders of the shoulder. When a history of visceral disease or evidence of severe cervical intraforaminal constriction is presented, the probability of incipient or incomplete reflex dystrophy must be suspected, appearing in many cases as the fore-runner of the complete clinical picture. The onset of hand signs usually resolves any doubts and completes the evidence of the shoulder-hand syndrome. In some of the patients with prolonged shoulder disability scapulohumeral fixation seems to develop.

The chief resemblance to the scalenus syndrome lies in the tenderness of the scalenus muscles in some of these patients, along with other points of soreness in the neck and shoulder, with weakness of the grip when the hand is swollen. Injection of the scalenus anticus muscle with procaine has proved ineffective. In the rare cases reported of scalenus anticus syndrome associated with hand signs similar to those in reflex dystrophy, it is quite likely that compression of the cords of the brachial plexus or of the subclavian artery has provoked reflex neurovascular symptoms as a complication. The possibility that the swelling of the hand represents partial occlusion of an anomalous subclavian vein running beneath the scalenus anticus muscle, instead of over it, was not confirmed in one patient subjected to exploration.

The appearance of the hand and fingers in the shoulder-hand syndrome is merely suggestive of rheumatoid disease in the early stages, particularly atypical rheumatoid arthritis. The swelling of the hand and digits is uniform, affecting all of them diffusely, rather than being limited to the periarticular tissues of one or merely several metacarpophalangeal or proximal interphalangeal joints. Tenderness to palpation, too, is generalized, and it is elicited anywhere on the hand. The persistent homolateral involvement of the shoulder and hand without symptoms in other joints on the same or on the opposite side of the body is unlike the behavior of rheumatoid arthritis. Only one of our patients seen in early phase I showed an increased sedimentation rate which soon became normal despite the progression of her condition. Even in the early stages of reflex disorders, the patients are afebrile and we have not found a leukocytosis.

Gout is simulated in very early hand involvement, by severe, painful, pinkish or pale swelling of the whole hand. The repeatedly normal blood uric acid, the unresponsiveness to therapy for gout, and surely a history of trauma or evidence of high visceral disease or other etiologic factors already stated, should suggest the probability of reflex dystrophy.

The appearance of the hand in the late stages has been regarded by some as the equivalent of scleroderma. This is not the place to consider the argument as to whether the latter condition may be due to reflex sympathetic changes. Our early cases have been characterized by a generalized swelling of the peripheral tissues, including the skin. Later, atrophy of all the structures of the fingers and hand develops gradually with, finally, striking trophic changes in the skin and underlying subcutaneous tissues. The skin becomes thin, smooth, glossy and in some patients presents remarkable hypertrichosis over the dorsal surface of the proximal phalanges. We have not observed the rigid, thickened cutis with pigmentation so characteristic of long-standing scleroderma. The frequent contractures of the palmar fascia and tendons is a typical concomitant in the late trophic stages of the shoulder-hand syndrome.

## TREATMENT OF THE SHOULDER-HAND SYNDROME

The management of these disorders until recently has proved largely unsatisfactory. Numerous forms of therapy, therefore, have been recommended for reflex dystrophy. The latest developments in sympathetic nerve block and in sympathetic surgery represent a great and highly effective advance in the treatment of these conditions.

### ORTHOPEDIC AND PHYSIO-THERAPEUTIC MEASURES

Immobilization of the affected parts in conjunction with the various modalities of physiotherapy—heat in all forms, heliotherapy and massage, have been utilized extensively. These measures, however, apart from giving temporary palliation, seem to exert little influence on the course of the disease. Oppenheimer,<sup>37</sup> on the other hand, employed short-wave diathermy to the cervical spine and in six of seven cases with swelling and atrophy of the hand secondary to cervical osteoarthritis he reported recovery. Our results with this form of treatment have not been impressive.

Manipulative procedures have been widely condemned. Manipulation of the shoulder, especially, in these cases is apt to be based on a misdiagnosis of bursitis, fibrositis and, possibly, scalenus anticus syndrome. The shoulder discomfort and disability frequently are regarded as symptoms complicating, or unrelated to, the hand signs. According to our experience such deductions usually represent a failure to correlate the salient features of the shoulder-hand syndrome.

### RADIATION THERAPY

Mumford<sup>57</sup> treated six cases of Sudeck's atrophy with high-voltage roentgen therapy to the affected extremity and reported good results in five. Hermann et al.,<sup>58</sup> however, subjected 18 patients with acute osteoporosis to radiation therapy, as outlined by Mumford and found that, while the pain was greatly lessened or relieved, the osseous changes, the disturbed function and the period of disability, were not materially influenced. We have had no experience with this type of treatment, although we have used radiation therapy directed to the cervico-dorsal region of the spine and to the sympathetic ganglia without benefit in three patients.

### BLOCK THERAPY

Block therapy with procaine or related anesthetic drugs has been recommended in the form of: (1) local injections at the "trigger points" and (2) infiltration of the appropriate sympathetic ganglia.

It would seem that local injections at the site of injury or irritation in post-traumatic reflex dystrophy should exert a beneficial action by blocking the afferent painful impulses, with consequent breaking of the "vicious circle"

already in action. Repeated local procaine injections of the injured area, however, have proved unsatisfactory in many instances. These unfavorable results arise usually from the difficulty in locating the "trigger points" exactly and from the widespread nature of the dystrophic symptoms and signs.

Excellent results have been reported from paravertebral sympathetic infiltration with procaine or related substances for reflex dystrophy of varied etiology. For example, of eight patients treated only with repeated sympathetic blocks, de Takats<sup>8</sup> observed complete recovery in seven, and partial recovery in one. Evans<sup>35</sup> reported arrest of symptoms or considerable improvement in all of 12 patients treated only with sympathetic blocks.

The newer technics of administering stellate and upper dorsal ganglion blocks by the anterior or anterolateral approaches, without necessitating hospitalization, constitute real progress in these therapeutic procedures.<sup>50</sup> In addition to sympathetic ganglion infiltration, brachial plexus block has been employed by us. Following plexus block shoulder disability improves often, but the hand signs are not influenced by this procedure. Adequate sympathetic response evidently cannot be effected by this approach. Shoulder signs resolve spontaneously much more often than the hand changes, so that treatment must be based on the responsiveness of these most serious features lest trophic alterations develop, after which repeated sympathetic block is not as apt to be successful as in the early phase.

### SURGERY

Sympathetic surgery is employed in reflex dystrophy, when repeated sympathetic blocks give only partial relief of symptoms, or when the response is effective but not lasting. The patient's general condition must be suitable. Several procedures are available: periarterial sympathectomy, sympathetic ramisection and ganglionectomy. Leriche,<sup>40</sup> Fontaine and Hermann<sup>50</sup> recommended the first operation when the disease is localized, and ganglionectomy when the process is more widespread. They reported good results with these operations. The success of periarterial sympathectomy and sympathetic ganglionectomy in these conditions has been confirmed in the exhaustive studies of de Takats.<sup>5-8</sup> He obtained complete recovery in eight of 12 patients so treated, and improvement in four. Evans<sup>35</sup> reported a satisfactory outcome in 22 of 29 patients who underwent sympathectomy. If sympathectomy fails, and pain continues unrelieved, anterolateral cordotomy and possibly sensory denervation of the cortex merit consideration, usually for intractable causalgia.<sup>44</sup>

Recently tetraethyl ammonium salts which cause blockade of the autonomic ganglia, have been suggested for pre-surgical therapeutic tests and for treatment of the causalgic states.<sup>60</sup> It is as yet too early to evaluate this mode of therapy.

## THERAPEUTIC RECOMMENDATIONS

Precise conclusions from our own experience with therapy will be published in detail elsewhere.<sup>58</sup> From the data on hand, however, it would appear that the treatment of choice for *Phase I* is stellate, and possibly also upper dorsal, sympathetic ganglion block. For *Phase II* this treatment is worth a trial. Even in *Phase III* it may at least provide relief of pain, especially when surgery is contraindicated by the general condition of cardiacs and hemiplegics. The desirable time for sympathectomy is during *Phase II* or earlier.

Spontaneous recovery from shoulder disability and pain especially, and in some cases also from the trophic changes, may occur before, or during, this stage. The ultimate course of any individual, however, is unpredictable. Failure to initiate proper treatment as early as possible frequently subjects the patient to the eventual hazard of more drastic measures or to irreversible, disabling alterations in the extremity.

From the onset through *Phase II*, therefore, we employ repeated sympathetic blocks with procaine or similar substances. When these give only partial relief of symptoms, or if the benefits prove only temporary, sympathetic surgery is indicated, provided the patient's general condition permits. Sympathetic blocks serve in that way not only as a method of treatment, but also as a therapeutic test for the proper selection of cases likely to respond to sympathectomy. When repeated sympathetic blocks, properly performed, are completely unsuccessful, it is uncertain whether sympathectomy will prove any more effective in relieving the symptoms. In *Phase III* sympathetic block for pain supplemented by intensive physical rehabilitation measures within the limits of the patient's reserve are warranted to retain, possibly to increase, the degree of function of the dystrophic extremity. Following relaxation by heat, special exercises to maintain mobility of the joints are employed by us at all stages when they do not provoke additional discomfort. In the late cases rehabilitation by retraining of muscular and digital function may reduce the disability.

## RELAPSES

Only one of the patients in our series gave a history of a previous attack of idiopathic painful swelling of the hand. It cleared up spontaneously over several months without any residual changes. About five months later she developed the shoulder-hand syndrome which resolved following three stellate blocks in the course of two weeks. This patient recently again presented a spontaneous, acute swelling of the hand alone, about seven months after treatment, which cleared up after one block. Obviously the incidence of relapses may prove greater than the present limited follow-up period reveals.

## SUMMARY

1. A number of seemingly different disorders, frequently involving the upper extremity, including the idiopathic shoulder-hand syndrome, described in the surgical and medical literature as separate entities appear to be closely related.

2. Although their etiology or precipitating factor varies, these conditions exhibit clinical features which are quite similar and the underlying mechanism seems to be identical, a reflex neurovascular dystrophy.

3. The different disorders embraced in reflex dystrophy of the upper extremity present either incomplete or complete signs of the neurovascular reaction of which the shoulder-hand syndrome constitutes the most complete picture.

4. The variable clinical features and the differences in the severity of symptoms probably are due to different degrees of reflex neurovascular and motor reaction.

5. Among these clinical pictures of reflex dystrophy, especially the idiopathic shoulder-hand syndrome, the shoulder disability and hand signs are often not correlated in the diagnosis, and are apt to be given separate diagnoses for the shoulder disability and for the hand signs.

6. The current neurophysiologic concept of "a vicious circle" mediated through an internuncial pool of active stimuli in the cord, provoked and maintained by the primary precipitating condition, explains the mechanism common to all forms of reflex (neurovascular) dystrophy, regardless of etiology. It serves as a useful working basis for the present therapeutic approach.

7. Treatment by sympathetic interruption (with stellate and upper dorsal ganglion block or surgery) is effective in a great number of all etiologic varieties, in that way confirming the common identity of the underlying mechanism.

8. Therapeutic results depend on the phase or stage of the disorder and the selection of the proper procedures.

## BIBLIOGRAPHY

1. MITCHELL, S. W., MOREHOUSE, G. R., and KEEN, W. W.: Gunshot wounds and other injuries of nerves, 1864, J. B. Lippincott, Philadelphia, 164 pages.
2. LIVINGSTON, W. K.: Pain mechanisms: a physiologic interpretation of causalgia and its related states, 1943, The Macmillan Company, New York.
3. HOMANS, J.: Minor causalgia: a hyperesthetic neurovascular syndrome, *New Eng. Jr. Med.*, 1940, ccxxii, 870-874.
4. NOBLE, T. P., and HAUSER, E.: Acute bone atrophy, *Arch. Surg.*, 1926, xii, 75-94.
5. MILLER, D. S., and DE TAKATS, G.: Post-traumatic dystrophy of the extremities—Sudeck's atrophy, *Surg., Gynec. and Obst.*, 1941, lxxv, 558-581.
6. DE TAKATS, G., and MILLER, D. S.: Post-traumatic dystrophy of the extremities—a chronic vasodilator mechanism, *Arch. Surg.*, 1943, xlv, 469-479.



7. DE TAKATS, G.: Nature of painful vasodilatation in causalgic states, *Arch. Neurol. and Psych.*, 1943, 1, 318-326.
8. DE TAKATS, G.: Causalgic states in peace and war, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 699-704.
9. SUDECK, P.: Ueber die akute entzündliche Knochenatrophie, *Arch. f. klin. Chir.*, 1900, lxii, 147-156.
10. SUDECK, P.: Ueber die akute reflektorische Knochenatrophie nach Entzündungen und Verletzungen an den Extremitäten und ihre klinische Erscheinungen, *Fortschr. a. d. Geb. Röntgenstr.*, 1901-1902, v, 277-293.
11. SUDECK, P.: Ueber die akute (trophoneurotische) Knochenatrophie nach Entzündungen und Traumen der Extremitäten, *Deutsch. med. Wchnschr.*, 1902, xxviii, 336-338.
12. SUDECK, P.: Die Kollateralen Entzündungsreaktionen an den Gliedenassen (sog. akute Knochenatrophie), *Arch. f. klin. Chir.*, 1938, cxci, 710-753.
- 13a. OSLER, W.: Lectures on angina pectoris and allied states, 1897, Appleton, N. Y., p. 50 (called to our attention by Max Trubek).
- 13b. HOWARD, T.: Cardiac pain and periarthritides of the shoulder, *Med. Jr. and Rec.*, 1930, cxxxi, 364-365.
- 13c. SHAPIRO, E., LIPKIS, M. L., and KAHN, J.: "Trophic" ulcers of the hands complicating myocardial infarction, *Am. Jr. Med. Sci.*, 1947, ccxiv, 288.
14. LIBMAN, E.: Symposium: angina pectoris with special reference to coronary artery disease, *Bull. N. Y. Acad. Med.*, 1935, xi, 427.
15. EDEIKEN, J., and WOLFERTH, C. C.: Persistent pain in the shoulder region following myocardial infarction, *Am. Jr. Med. Sci.*, 1936, cxci, 201-210.
16. BOAS, E. P., and LEVY, H.: Extracardiac determinants of the site and radiation of pain in angina pectoris with special reference to shoulder pain, *Am. Heart Jr.*, 1937, xiv, 540-554.
17. LEECH, C. B.: Painful shoulder in association with coronary artery disease, *Rhode Island Med. Jr.*, 1938, xxi, 104-106.
18. ERNSTENE, A. C., and KINELL, J.: Pains in the shoulder as a signal of myocardial infarction, *Arch. Int. Med.*, 1940, lxvi, 800-806.
19. ASKEY, J. M.: The syndrome of painful disability of the shoulder and hand complicating coronary occlusion, *Am. Heart Jr.*, 1941, xxii, 1-12.
20. JOHNSON, A. C.: Disabling changes in the hand resembling sclerodactylia following myocardial infarction, *Ann. Int. Med.*, 1943, xix, 433-456.
21. DUPUYTREN, G.: De la retraction des doigts par suite d'une affection de l'aponeurose palmaire; operation chirurgicale qui convient dans ce cas, *Jr. Univ. et hebdom. de med. et chir. prat.*, 1832, 25, v, 348-365.
22. KANAVAL, A. B., KOCH, S. L., and MASON, M. L.: Dupuytren's contracture with a description of the palmar fascia, a review of the literature and a report of twenty-nine surgically treated cases, *Surg., Gynec. and Obst.*, 1929, xlviii, 145-190.
23. MEYERDING, H. W., BLACK, J. R., and BRODERS, A. C.: The etiology and pathology of Dupuytren's contracture, *Surg., Gynec. and Obst.*, 1941, lxxii, 582-590.
24. HORWITZ, T.: Dupuytren's contracture—a consideration of the anatomy of the fibrous structures of the hand in relation to this condition, with an interpretation of the histology, *Arch. Surg.*, 1942, xlv, 687-706.
25. NIPPERT, A.: Konstitution, Stoffwechsel und Dupuytren'sche Kontraktur, *Deutsch. Ztschr. f. Chir.*, 1929, ccxvi, 289-292.
26. POWERS, H.: Dupuytren's contracture one hundred years after Dupuytren: interpretation, *Jr. Neurol. and Ment. Dis.*, 1934, lxxx, 386-409.
27. Quoted by Kennard and Bucy.<sup>29, 30</sup>
28. GOWERS, W. R.: A manual of diseases of the nervous system, 1888, J. and A. Churchill, London, Vol. 2, p. 77.

29. KENNARD, M. A.: Vasomotor disturbances resulting from cortical lesions, *Arch. Neurol. and Psychiat.*, 1935, lxxxiii, 537-545.
30. BUCY, P. C.: Vasomotor changes associated with paralysis of cerebral origin, *Arch. Neurol. and Psychiat.*, 1935, xxxiii, 30-52.
31. LUHAN, J. A.: Hemiedema in cases of hemiplegia, *Arch. Neurol. and Psychiat.*, 1936, xxxvi, 42-57.
32. ELLIS, L. B., and WEISS, S.: Vasomotor disturbances and edema associated with cerebral hemiplegia, *Arch. Neurol. and Psychiat.*, 1936, xxxvi, 362-372.
- 33a. STEINBROCKER, O.: Painful homolateral disability of shoulder and hand with swelling and atrophy of hand, *Ann. Rheum. Dis.*, 1947, vi, 80; The shoulder-hand syndrome, *Am. Jr. Med.*, 1947, iii, 402.
- 33b. STEINBROCKER, O., SPITZER, N., and FRIEDMAN, H. H.: The shoulder-hand syndrome (reflex dystrophy of the upper extremity), Exhibit, Post-Grad. Medicine. (In press.)
34. BINGHAM, J. A. W.: Causalgia of the face: two cases successfully treated by sympathectomy, *Brit. Med. Jr.*, 1947, i, 804-805.
35. EVANS, J. A.: Sympathectomy for reflex sympathetic dystrophy, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 620-623; Reflex sympathetic dystrophy: report on 57 cases, *Ann. Int. Med.*, 1947, xxvi, 417-426.
36. MARQUES, S.: Herpes zoster e Osteodistrofia, *Arg. brasil. de cir. e ortop.*, 1938, vi, 77-80.
37. OPPENHEIMER, A.: The swollen atrophic hand, *Surg., Gynec. and Obst.*, 1938, lxvii, 446-454.
38. KELLY, M.: The nature of fibrositis. II. A study of the causation of the myalgic lesion (rheumatic, traumatic, infective), *Ann. Rheumat. Dis.*, 1946, v, 69-77.
39. COLLINS, V. J., FOSTER, W. L., and WEST, W. J.: Vasomotor disturbances in poliomyelitis with special reference to treatment with paravertebral sympathetic block, *New Eng. Jr. Med.*, 1947, ccxxxvi, 694-697.
40. KEHL, K. C.: Dupuytren's contracture as a signal to coronary artery disease and myocardial infarction, *Ann. Int. Med.*, 1943, xix, 213-223.
41. SWEETAPPLE, H. A.: Sudeck's atrophy, *Med. Jr. Australia*, 1946, ii, 581-584.
42. WRIGHT, I. S.: The neurovascular syndrome produced by hyperabduction of the arms, *Am. Heart Jr.*, 1945, xxix, 1.
43. TELFORD, E. D., and MOTTERSHEAD, S.: The "costoclavicular syndrome," *British Med. Jr.*, 1947, 325.
44. FALCONER, M. A., and WEDELL, G.: The costoclavicular syndrome, *Lancet*, 1943, ii, 539.
45. DE GUTTIEREZ-MAHONEY, C. G.: The treatment of painful phantom limb by removal of post-central cortex, *Jr. Neurosurg.*, 1946, i, 156.
46. WOLFF, JULIUS: Ueber einen Fall von Ellenbogengelenks-Reaktion, *Arch. f. klin. Chir.*, 1877, xx, 771-795.
47. WOLFF, JULIUS: Ueber trophische Störungen bei primären Gelenksleiden, *Berl. klin. Wchnschr.*, 1883, xx, 418, 422-426.
48. KÜMMELL, H.: Ueber die traumatischen Erkrankungen der Wirbelsäule, *Deutsch. med. Wchnschr.*, 1895, xxi, 180-181.
49. KIENBÖCK, A.: Ueber Knochenveränderungen bei gonorrhöischer Arthritis und akute Knochenatrophie überhaupt, *Wien. klin. Wchnschr.*, 1903, xvi, 57-63, 99-105.
50. LERICHE, R.: The surgery of pain, 1939, Williams and Wilkins, Baltimore.
51. FONTAINE, R., and HERMANN, L. G.: Post-traumatic painful osteoporosis, *Ann. Surg.*, 1933, xcvi, 26-61.
52. GURD, F. B.: Post-traumatic acute bone atrophy—a clinical entity, *Arch. Surg.*, 1936, xxxii, 273-291.
53. HERMANN, L. G., and CALDWELL, J. A.: Diagnosis and treatment of post-traumatic osteoporosis, *Am. Jr. Surg.*, 1941, 511-630.

53. HERMANN, L. G., REINEKE, H. G., and CALDWELL, J. A.: Post-traumatic painful osteoporosis: a clinical and roentgenological entity, *Am. Jr. Roent. and Rad. Ther.*, 1942, xlvii, 353-361.
54. WECHSLER, ISRAEL S.: A textbook of clinical neurology, 4th Ed., 1939, W. B. Saunders Company, Philadelphia, p. 366.
55. LORENTE DE NÓ, R.: Analysis of the activity of the chain of internuncial neurons, *Jr. Neurophys.*, 1938, i, 207.
56. KEY, A. J., FISCHER, F., and ELZINGE, E.: Local atrophy of bone, *Arch. Surg.*, 1934, xxviii, 936-947.
57. MUMFORD, E. B.: Roentgentherapy in acute osteoporosis—a new type of treatment, *Jr. Bone and Joint Surg.*, 1938, xx, 949.
58. STEINBROCKER, O., SPITZER, N., and FRIEDMAN, H. H.: The treatment of the shoulder-hand syndrome (reflex dystrophy of the upper extremity), with special reference to sympathetic block, *Anesthesia and Analgesia*. In press.
59. FINDLAY, T., and PATZER, R.: The treatment of herpes zoster by paravertebral-procaine block, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1217.
60. BERRY, R. L., CAMPBELL, K. N., LYONS, R. H., MOE, G. K., and SUTHER, M. R.: The use of tetraethylammonium in peripheral vascular disease and causalgic states, *Surgery*, 1946, xx, 525-535.

# THE ACTION OF NEOSTIGMINE IN SUPRAVENTRICULAR TACHYCARDIAS \*

By SAMUEL WALDMAN, M.D., and LOUIS PELNER, M.D.,  
*Brooklyn, New York*

NEOSTIGMINE has been used successfully in the treatment of supraventricular tachycardias.<sup>1, 2, 3, 4, 5, 6</sup> Its action is predicated upon the cholinergic activity of this drug, which in these cases effects its often dramatic action through the vagus nerve. By inhibiting the action of cholinesterase at the myoneural junction, it permits the action of choline to exert its full effect. Study of the action of neostigmine in tachycardias has made it evident that its action is of somewhat specific value in treating sinus tachycardias, paroxysmal auricular tachycardias, and paroxysmal nodal tachycardias. By correcting the chemical and physical imbalance which has resulted in the accelerated heart rate, neostigmine exerts a definitive effect. Waldman and Moskowitz<sup>1</sup> first demonstrated its effectiveness in sinus tachycardia and in paroxysmal auricular tachycardia in 1941. These findings were soon confirmed by Pelner<sup>2</sup> who also felt that the carotid sinus was made more sensitive by neostigmine. In 1944, again, Waldman and Moskowitz showed excellent results in 18 cases of sinus tachycardia, not associated with organic disease. Recently<sup>5</sup> in studying the electrocardiographic effects of neostigmine it was found that the cardiac rate was slowed in 86 patients with all types of tachycardias including auricular fibrillation and auricular flutter. Our experience has not confirmed a slowing effect in auricular fibrillation and auricular flutter.

## THE VAGUS NERVE AND THE INNERVATION OF THE HEART (Figure 1)

The left and right vagus nerves are cardio-inhibitory in action and carry fibers by way of the parasympathetic division of the autonomic nervous system from the cardio-inhibitory centers in the medulla to the supraventricular region of the heart. The cardiac vagal fibers separate from the main trunk, in the neck, between the origin of the superior and inferior laryngeal branches. The fibers then, in combination with the fibers of the accelerator nerves enter into the formation of the superficial and deep cardiac plexuses. Thence they go directly to the heart.

Fibers from the right nerve terminate around ganglion cells in auricular tissue in the region of the sino-auricular node. These cells serve as relay stations in the transmission of the vagal influence. Their axons enter the node and form a plexus around muscle cells in sino-auricular tissue. The left nerve enters into similar relationships with the auriculo-ventricular node.

\* Read before the Eastern Section of the American Federation for Clinical Research at New York Hospital on December 12, 1947.

Its terminations arborize around ganglion cells in the inter-auricular septum which send axons to the muscular elements of the nodal tissue. Although the right nerve is chiefly distributed to the sino-auricular node and the left to the auriculo-ventricular node, each node receives some filaments from the opposite nerve.

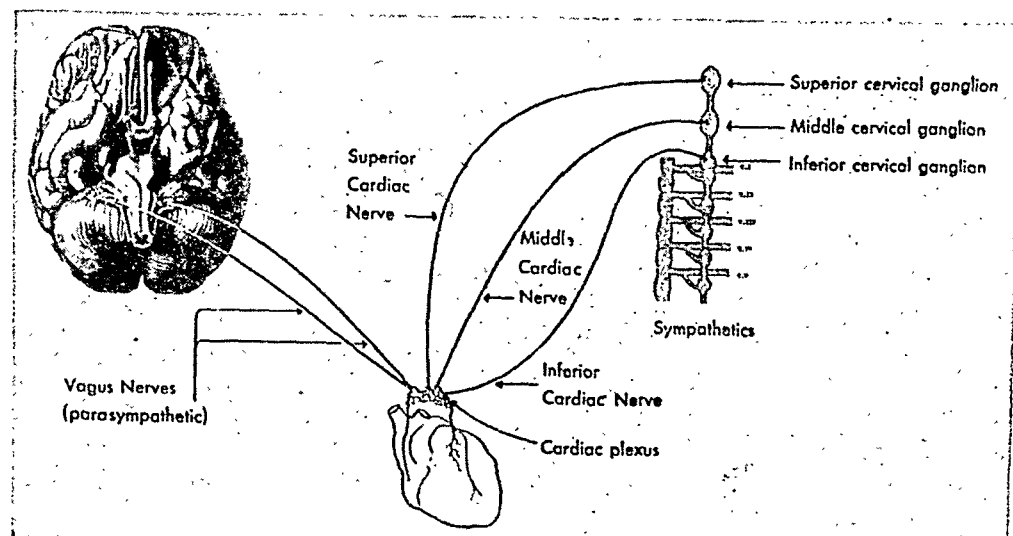


FIG. 1. Innervation of the heart.

Stimulation of the vagus nerve causes slowing of the heart mainly by the lengthening of diastole. Systole is little affected. The vagus exerts its effect on the heart by action on the auricular muscle, the sino-auricular node, and the auriculo-ventricular node. There is no direct action on the ventricular muscle. The ventricular slowing is secondary to auricular slowing, or stoppage, or to depression of auriculo-ventricular conduction (block). The right and left vagus nerves differ in their action. Stimulation of the right vagus nerve results mainly in slowing of the auricular beat and thus reduces the ventricular rate. Stimulation of the left nerve causes ventricular slowing by depressing auriculo-ventricular conduction and if strong enough may block auricular impulses.

From this anatomical discussion and from the knowledge of the physiologic action of neostigmine it becomes evident that the effect of neostigmine should be on the sino-auricular node, auricular muscle and auriculo-ventricular node. Apparently this is so, according to the studies described in this paper. It is believed that the basis of some cardiac disturbances is primarily chemical changes in heart muscle without histologic changes.<sup>7</sup> Raab<sup>8</sup> believes that some common forms of heart disease are due to biochemical changes in which the sympathomimetic amines play a dominant rôle. Katz et al.<sup>9</sup> also feel that cardiac arrhythmias may be dependent upon an imbalance of the autonomic nervous system or the endocrine system. Emotional disturbances may create imbalance in these systems. The tachy-

cardias are probably produced in the same way; and neostigmine, by correcting the imbalance through action on the vagus, restores the heart to normal rhythm.

In the case of sinus tachycardia, neostigmine decreases the rate of impulse formation at the sino-auricular node. This is evident by the increased TP interval (figures 2 and 3) due to the slower sino-auricular node impulse formation. This is effected through action of both vagi, predominantly the right which contacts the sino-auricular area where the biochemical change probably has occurred.

In paroxysmal auricular tachycardia, the ectopic focus is somewhere in the auricle, not in the sino-auricular node. Stimulation of the right vagus would slow the sinus rate but might not slow the rate of impulse formation issuing from an ectopic focus in the auricle. However, stimulation of the left vagus could slow the ventricular rate by decreasing conductivity at the auriculo-ventricular node and thus produce a block of some degree. This actually takes place (cases 3 and 4, figures 4 and 5).

In paroxysmal nodal tachycardia, again, the left vagus effect would be expected to be the predominant factor for the same reason. That this occurs is again shown by electrocardiographic studies (case 5 and figure 6).

We thus see that a selective predominant vagus stimulating effect, as would be theoretically suggested, actually takes place and by this means supraventricular tachycardias are corrected by the action of neostigmine. In sinus tachycardias, it slows impulse formation at the sino-auricular node; in paroxysmal auricular and nodal tachycardias it creates a degree of block in the auriculo-ventricular bundle and soon normal rhythm is reestablished.

In the present study, the same methods were used as were previously employed.<sup>1, 4</sup> An initial complete electrocardiogram was taken. Then the injection of 1 mg. neostigmine methylsulfate was given and tracings were taken every five minutes in Lead II for 20 minutes. It was found before that the full effect is evident within 20 minutes, or not at all. Goldfinger and Wosika<sup>5</sup> also found 20 minutes the optimal time for response.

## ILLUSTRATIVE CASES

### *Sinus Tachycardias*

*Case 1.* S. F., female, aged 36, married, was seen during an attack of sinus tachycardia, complaining of severe palpitation and pain in the left chest. The past history was irrelevant except for the family history. Her father had died two years before, following a second attack of myocardial infarction due to coronary occlusion. Her mother has severe hypertension. The patient was quite emotional and with this family history was quite cardio-sensitive so that emotional disturbances focused on the heart. This is not an uncommon condition.<sup>9</sup>

Physical examination, fluoroscopy and electrocardiogram (figure 2A, B, C, D) of the patient revealed no evidence of heart disease. The pulse rate during the attack varied from 115 to 125, the blood pressure was 160 mm. Hg systolic and 90 mm. diastolic.

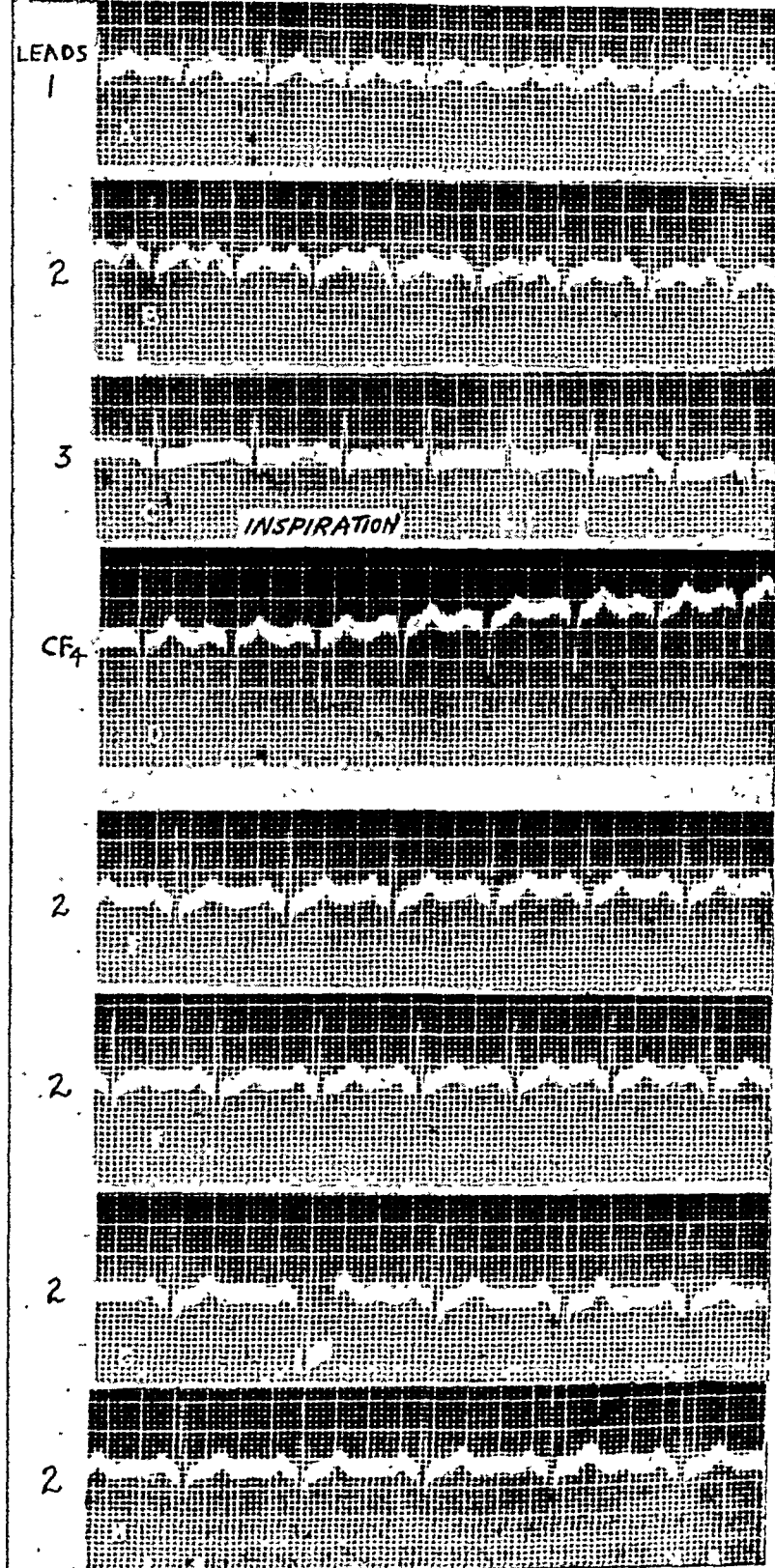


FIG. 2. Case 1.

S. F., female, no organic heart disease. A, B, C, D—standard and precordial leads showing a sinus tachycardia of 115 to 125 before the injection of 1 mg. neostigmine. E—five minutes after injection of 1 mg. neostigmine methylsulfate, rate is reduced to 96. F—10 minutes after the injection, rate is still 96. G—15 minutes after the injection the rate is 79. H—20 minutes after the injection the rate is 75.

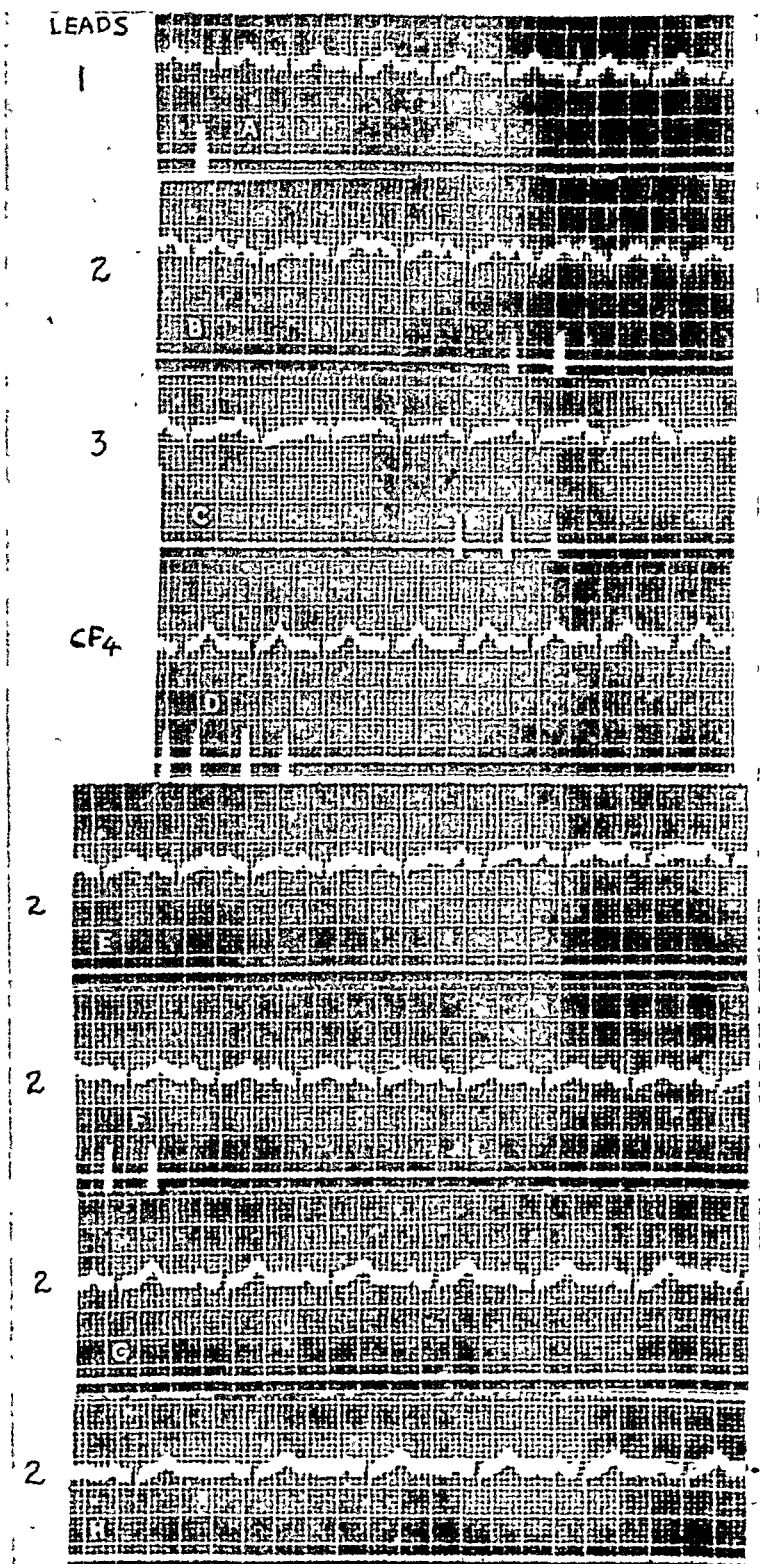


FIG. 3. Case 2.

R. G., female, no organic heart disease. A, B, C, D—standard and precordial leads showing attack of sinus tachycardia. Rate is 136. E—five minutes after injection of 1 mg. neostigmine methylsulfate rate slowed to 115. F—10 minutes after the injection, the rate is 107. G—15 minutes after injection the rate is 88. H—20 minutes after injection the rate is 83.



The patient was given an injection of 2 c.c. of neostigmine methylsulfate (1:2000 = 1 mg.) intramuscularly, and electrocardiograms were taken at five minute intervals for the next 20 minutes using Lead II as the recording lead.

Within five minutes the rate had slowed to 96 (figure 2E), in 10 minutes it was still 96 (figure 2F), in 15 minutes the rate was 79 (figure 2G), and in 20 minutes it was 75 (figure 2H). The patient felt much better, and was relieved of her anxiety and palpitation.

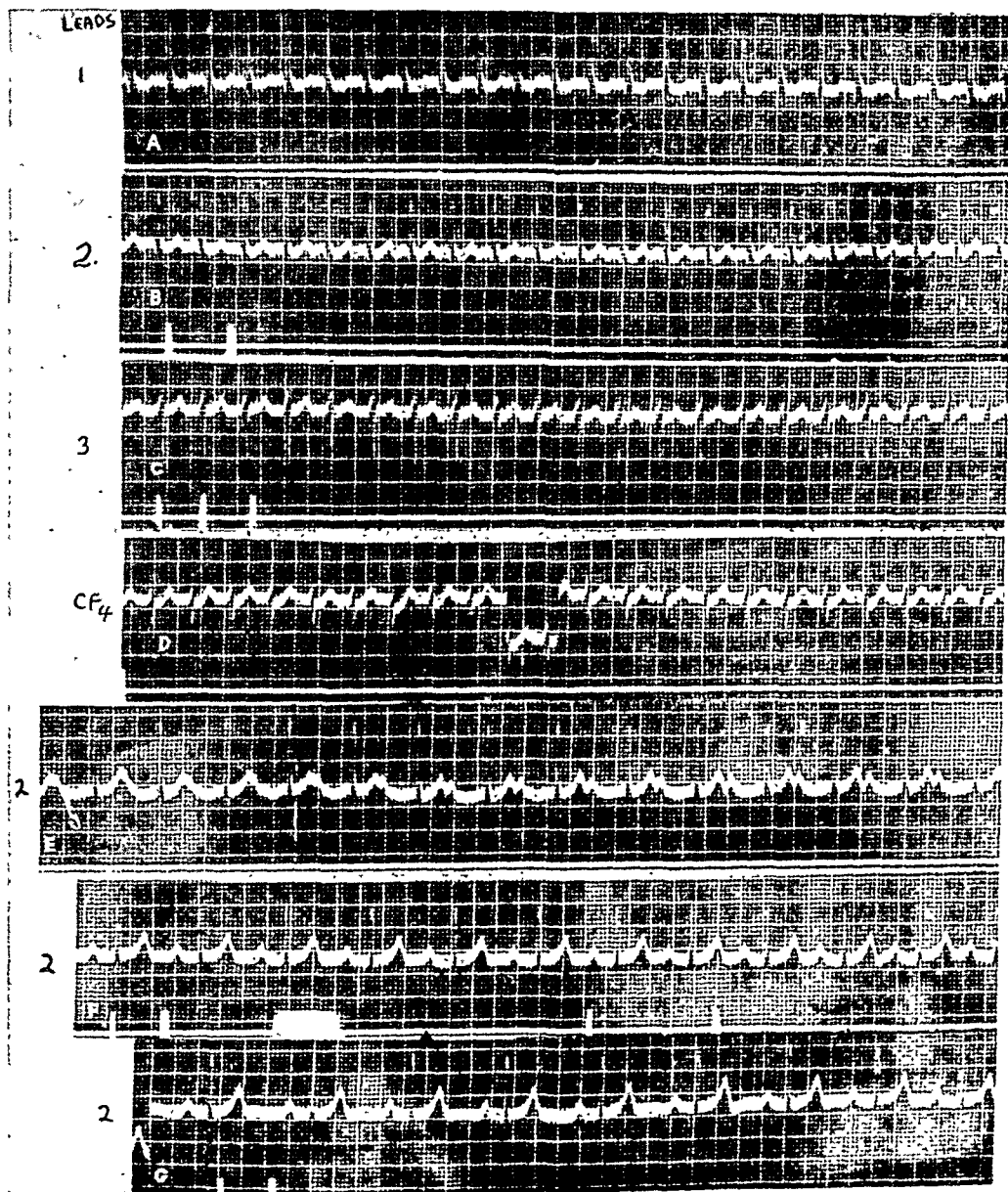


FIG. 4. Case 3.

L. F., female, rheumatic heart disease. A, B, C, D—standard and precordial leads exhibit a paroxysmal auricular tachycardia at the regular rate of 166. E—five minutes after injection of 1 mg. neostigmine the ventricular rate slowed to 94 to 100, and PR interval was 0.36 second (first degree heart block). F—In 10 minutes the rate varies from 79 to 88 with PR interval of 0.24 second. G—after 15 minutes the rate is 71 and the PR interval is 0.22 second.

*Case 2.* R. G., female, aged 27, married, noted recent frequent attacks of palpitation associated with nervousness. These were increasing in severity and duration and caused insomnia and anorexia, associated with fretfulness. She appeared in the office with a pulse rate of 136, blood pressure 154/80. Physical and fluoroscopic examination revealed no evidence of organic heart disease. She was extremely agitated. Carotid sinus pressure caused only temporary slowing of the heart. Reassurance was of no avail. An injection of 1 mg. neostigmine methylsulfate was given intramus-

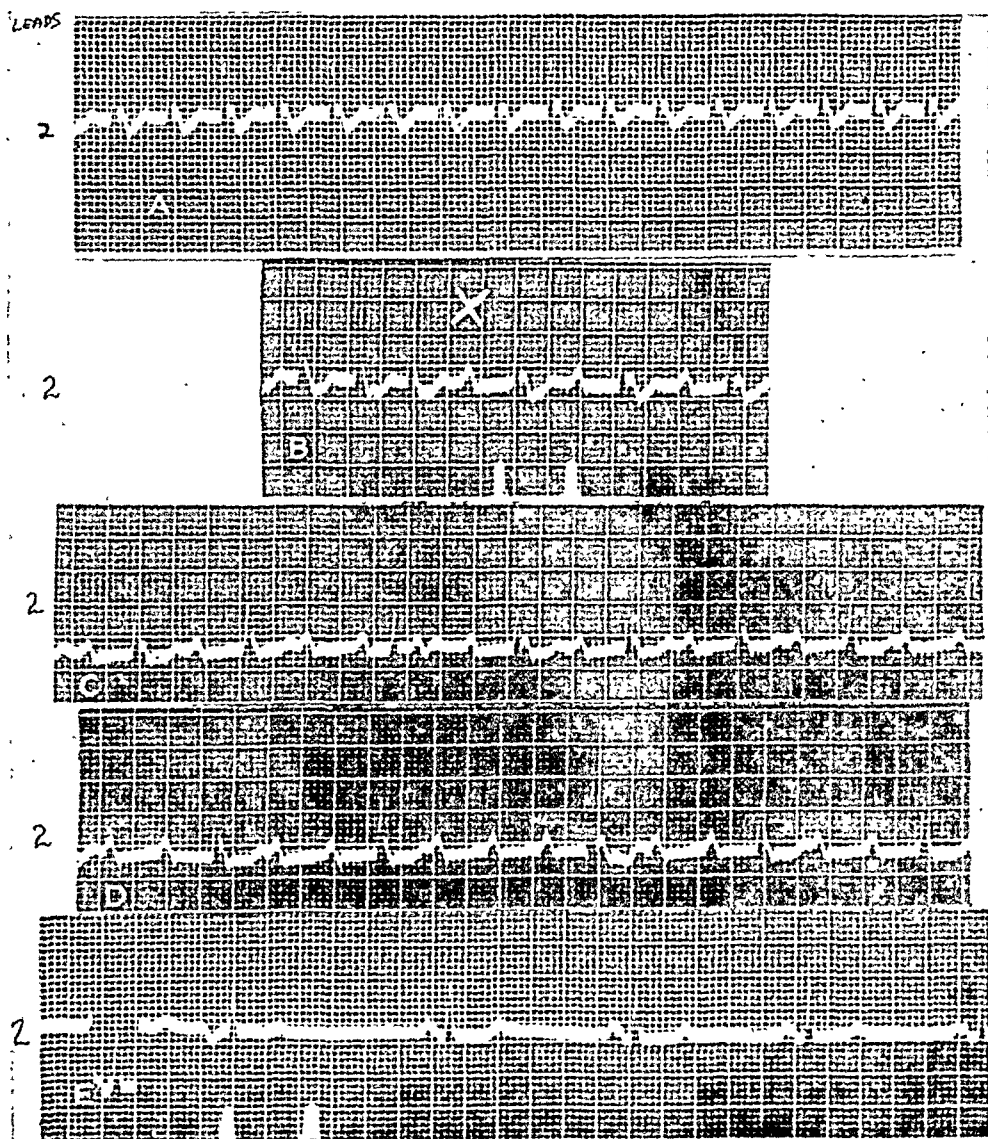


FIG. 5. *Case 4.*

R. R., 47, female, with long-standing rheumatic heart disease. Figures are of Lead II. A—before injection—paroxysmal auricular tachycardia with a rate of 188. B—3 minutes after injection of 1 mg. neostigmine the auricular rate is 188, ventricular rate is 94. "X" marks onset of 2:1 block. C—8 minutes after injection, varying 3:1, 2:1 block is present. D—33 minutes after injection, varying 3:1 to 4:1 block is present. Auricular rate is 188, ventricular rate averages 60. E—sinus bradycardia (56) 2 days later, auricular premature contraction present. (Reprinted from Medical Record, 1941, cliii, 134.)

LEADS

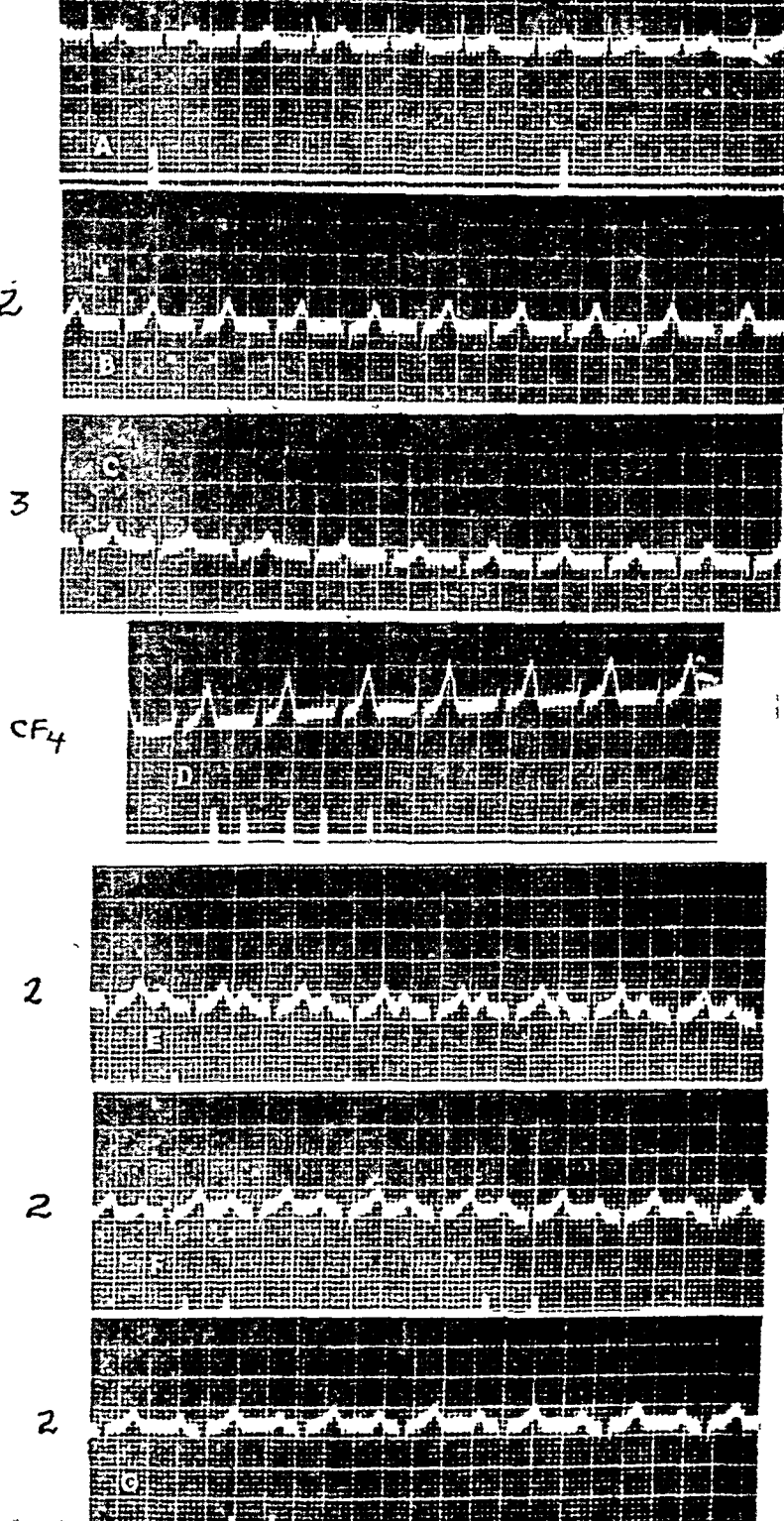


FIG. 6. Case 5.

F. A., female, rheumatic heart disease. A, B, C, D—standard and precordial leads show a nodal tachycardia, rate 136. E—five minutes after injection of 1 mg. neostigmine methylsulfate the rate has dropped to 115, PR interval 0.21 second. F—10 minutes later the rate is 100, PR interval 0.18 second. G—15 minutes later the rate is 88. PR is 0.16 second.

cularly. The electrocardiogram before injection is seen in figure 3 A, B, C, D, the rate being 136. In five minutes the rate slowed to 115 (figure 3 E), in 10 minutes to 107 (figure 3 F), in 15 minutes to 88 (figure 3 G), and in 20 minutes to 83 (figure 3 H). Following this response, the patient felt much better and became receptive to reassurance as to the benign nature of the attacks. Further attacks then were minimal, created less disturbance to the patient, and finally attacks failed to recur.

From the electrocardiographic studies in these cases, it is evident that the slowing of the heart rate was dependent upon a decrease in the rate of impulse formation at the sino-auricular node. This is apparent by the increase in the TP interval. Neostigmine, therefore, in these instances, produced the slowing effect by stimulation of the vagus nerve (especially the right) which has its terminations mainly at the sino-auricular node, where the rate of impulse formation was excessively rapid. Probably by correcting a chemical imbalance, restoration of a normal rate was established.

### *Paroxysmal Auricular Tachycardia*

*Case 3.* L. F., 20 years old, married, female, was a known rheumatic cardiac with mitral stenosis and insufficiency and aortic stenosis and insufficiency. She had been having frequent recurrent attacks of palpitation which at times would last several days.

When seen at the office, she had a rapid regular tachycardia of 166 beats per minute. The electrocardiogram (figure 4A, B, C, D) showed a typical paroxysmal auricular tachycardia. Carotid sinus and ocular pressure were of no avail. One milligram of neostigmine was given intramuscularly. In five minutes, the tachycardia had slowed to 94-100. The electrocardiogram (figure 4E) showed a P-wave appearing on a T-wave and then breaking away into an individual P-wave. The PR interval during this change was 0.36 second (first degree auriculo-ventricular block). In 10 minutes the rate of the heart varied from 79 to 88 and the PR interval measured 0.24 second (figure 4F). In 15 minutes the rate was 71 (normal sinus rhythm) and the PR interval was 0.22 second (figure 4G).

This patient is still under the medical care of one of us (S. W.). Because of the frequently recurring attacks, attempts at prevention were made. Digitalization failed to prevent the attacks. Quinidine diminished their frequency. Since neostigmine injection repeatedly aborted the attacks and since previous experience<sup>4</sup> showed that oral medication helped some cases, the latter therapy was attempted. The patient was given neostigmine bromide, 0.015 gm., three times daily at equal intervals. Since October, 1945 when this regime was begun, she has had only a few, short lasting attacks. No attack was severe enough to require any additional medication, oral or parenteral. The patient volunteered the information that neostigmine bromide helped her more than quinidine or digitalis and she continues to take the neostigmine tablets despite the relatively higher cost.

In this case the neostigmine induced a heart block by vagal stimulation causing auriculo-ventricular block of first degree. Following this, the rhythm became normal.

*Case 4.* [This case has previously been reported<sup>1</sup> but is being used here to demonstrate another form of auriculo-ventricular block produced by neostigmine.]

R. R., female, single, aged 47, had rheumatic heart disease of 25 years' duration with mitral stenosis and insufficiency. She had had frequent attacks of tachycardia

which unnerved her despite her knowledge of their nature. The attack shown here occurred on July 27, 1940 and had lasted eight hours when the patient was seen. The rate was 188 beats per minute and the electrocardiogram demonstrated a paroxysmal auricular tachycardia (figure 5A). Other methods (digitalis, quinidine in maintenance doses, carotid sinus and eyeball pressure), having failed to prevent or terminate the attacks, one milligram of neostigmine methylsulfate was injected intramuscularly. In three minutes the ventricular rate dropped to 94, while the auricular rate persisted at 188; a 2:1 heart block had developed (figure 5B). There was marked relief with alleviation of the cyanosis which had been present. Five minutes later there was a 3:1, 2:1 block (figure 5C). For 33 minutes (figure 5D) the cardiac rhythm persisted with a block varying from 3:1 to 4:1. The auricular rate remained at 188, while the average ventricular rate dropped to 60. A graph taken two days later revealed a sinus bradycardia, rate 56, with occasional auricular premature contraction (figure 5E). It may also be noted that the P-waves were peaked during the period of block when they became easily visible, while they were low, wide and notched in the interval graph. This indicated an ectopic origin of the P-wave during the tachycardia, which is expected in paroxysmal auricular tachycardia. This patient had other similar episodes which responded, similarly with heart block, to injections of neostigmine methylsulfate.<sup>1</sup>

In this instance the cessation of the attack of paroxysmal auricular tachycardia was secondary to the induction of partial heart block by neostigmine. The heart block was of second degree with varying 2:1, 3:1 and 4:1 incomplete auriculo-ventricular block. We thus see that the neostigmine again was effective through vagal action, especially affecting the left vagus (which terminates mostly at the auriculo-ventricular bundle), and by producing the block corrects the imbalance and thus permits the resumption of normal sinus rhythm.

### *Paroxysmal Nodal Tachycardia*

*Case 5.* F. A., female, unmarried, age 22, had recurrent attacks of palpitation for the past two or three years. She was a known rheumatic cardiac with mitral stenosis and insufficiency. On the day the study was made, she had noted palpitation for the preceding five hours and could not relieve it with sedatives, rest and ice bags. At the onset of the test the pulse rate was 136 per minute. The electrocardiogram (figure 6A, B, C, D) showed a nodal (probably mid-nodal) tachycardia with a rate of 136 per minute. An injection of 1 mg. of neostigmine was given. In five minutes the rate dropped to 115 (figure 6E). A P-wave appeared with a PR interval of 0.21 second. A slight degree of first degree block was produced. In 10 minutes the rate was 100 and PR interval was 0.18 (figure 6F). In 15 minutes the rate was 88 with PR interval 0.16 second (figure 6G).

It is here apparent that the neostigmine effected its action through the vagus, on the auriculo-ventricular bundle. Here it produced a slight degree of block; and the sino-auricular node took over impulse formation. Within 15 minutes the block disappeared and normal sinus rhythm returned.

### SUMMARY

The anatomical and physiological relations of the vagus nerve and the action of neostigmine are discussed. In sinus tachycardia neostigmine re-

duces the rate by slowing impulse formation at the sino-auricular node through stimulation of the vagus, especially the right. In paroxysmal auricular and nodal tachycardias, it slows the heart rate by stimulating the vagus, especially the left, thus inducing incomplete heart blocks of varying degree. Five cases are presented to demonstrate this action of neostigmine methylsulfate in the treatment of supraventricular tachycardias.

### COMMENT

From this study it appears that neostigmine exerts a somewhat selective specific effect on supraventricular tachycardias, depending upon the site of origin. It exerts this action through the medium of vagal stimulation. It seems that this action adds credence to the currently growing concept that many functional and some organic disorders of the heart are of metabolic, or chemical origin secondary to disturbances in the autonomic and/or endocrine systems.

Part of the supplies used in this study was furnished through the courtesy of Messrs. Freeman and Handsman of Hoffmann-LaRoche, Inc., Nutley, N. J.

### BIBLIOGRAPHY

1. WALDMAN, S., and MOSKOWITZ, S. N.: The effect of prostigmin on supraventricular tachycardias, *Med. Rec.*, 1941, cliii, 134.
2. PELNER, L.: Prostigmin in paroxysmal tachycardia, *Med. Rec.*, 1941, cliii, 209.
3. BATTRO, A., SEGURA, R. G., and LANARI, A.: El prostigmin en el tratamiento de las taquicardias paroxisticas supraventriculares, *Medicina*, 1941, i, 4.
4. WALDMAN, S., and MOSKOWITZ, S. N.: The treatment of attacks of sinus tachycardia with prostigmin, *Ann. Int. Med.*, 1944, xx, 793.
5. GOLDFINGER, D., and WOSIKA, P. H.: The electrocardiographic effects of prostigmin, *Am. Jr. Med. Sci.*, 1946, ccxii, 418.
6. BELLET, S.: Diagnosis and treatment of cardiac arrhythmias, *Med. Clin. N. Am.*, 1946, 1307.
7. PALLARES, E. S., OROZCO, F. V., and RIVIERO, J. M.: Note on a pentose isolated from heart muscle, *Am. Heart Jr.*, 1947, xxxiii, 705.
8. RAAB, W.: Sympathomimetic amines in the heart muscle; their pathogenic and therapeutic significance, *Am. Heart Jr.*, 1947, xxxiii, 707.
9. KATZ, L. N., WINTON, S. S., and MEGIBOW, R. S.: Psychosomatic aspects of cardiac arrhythmias; a physiological dynamic approach, *Ann. Int. Med.*, 1947, xxxi, 261.

# OBSERVATIONS ON THE USE OF THE RESPIRATOR IN REFRACTORY STATUS ASTHMATICUS \*

By MORTON F. REISER, M.D., and EUGENE B. FERRIS, JR., M.D., F.A.C.P.,  
*Cincinnati, Ohio*

## INTRODUCTION

RECENT advances in our knowledge of the nature and management of bronchial asthma have contributed greatly to the intelligent handling and well being of patients afflicted with this disorder. Interim treatment oriented in relation to allergic,<sup>1</sup> psychiatric,<sup>2</sup> and physiologic<sup>3</sup> considerations has greatly increased the comfort of asthma sufferers, and has reduced the frequency of acute episodes of asthmatic breathing. For the acute attack the physician now has at his disposal a powerful armamentarium of anti-spasmodic and sedative drugs in addition to materials for effective inhalation therapy; yet a small number of patients suffering status asthmaticus fail to respond to the most heroic and carefully planned therapy available. It is the purpose of this communication to present a new therapeutic maneuver (use of the Drinker Respirator) which appears to be of value in the treatment of such cases.

## RATIONALE AND PATHOLOGICAL PHYSIOLOGY

The rationale of this therapeutic maneuver is based upon a consideration of the pathological physiology of asthma. In the obstructive dyspnea of asthma there is greater interference with expiration than with inspiration. This is suggested clinically by the prolongation of the act of expiration and the occurrence of wheezes and other signs of tubular narrowing primarily in the expiratory phase of respiration. In chronic asthma, the chest gradually expands and assumes more and more a position of deep inspiration, as chronic emphysema with its limitation of the range of respiratory excursion develops. In cases of acute intractable asthma (status asthmaticus) one can watch the development of acute emphysema with the chest expanding progressively with each inspiration, as the expiratory phase becomes increasingly more ineffective.

There seem to be several factors underlying this phenomenon of acute ballooning of the lungs. It should be remembered that normally inspiration is an active process, whereas expiration is passive, the air flowing outward because of the elastic recoil of the lungs and the diminution in chest volume attendant to relaxation of the diaphragms and inspiratory muscles. The only muscles that can play an active rôle in expiration are those of the ab-

\* Received for publication September 20, 1947.

From the Department of Internal Medicine, University of Cincinnati College of Medicine

dominal wall and the internal intercostals.<sup>4</sup> With obstruction during the inspiratory phase (as exists in the diffuse constant bronchiolar spasm of asthma), inspiration becomes more forcible resulting in a negative intrathoracic pressure greater than normal,<sup>5,6</sup> and air is able to pass into the alveoli through the constricted bronchioles. The constricted passageway, however, is more effective in blocking the outflow of air during expiration. Considering the difference in physiologic rôles, it is likely that the accessory muscles of expiration are less efficient and more fatigable than those of inspiration. Further, the elastic recoil of the lungs during expiration normally permits bronchial narrowing during this phase, and it has been noted during bronchoscopic examinations that the degree of narrowing is greater than normal in patients with asthma.<sup>8</sup> As a result of the lagging expiratory efficiency, with each breath more air is drawn into the alveoli than can be expelled and the lungs become literally "blown up."

When the bronchial constriction cannot be adequately lessened by means of antispasmodic and/or sedative and anesthetic measures, the primary therapeutic aim must be the maintenance of adequate oxygenation until relief of the respiratory obstruction can finally be achieved, or until spontaneous remission occurs. The use of 100 per cent oxygen or 80 per cent helium—20 per cent oxygen will often relieve the cyanosis (anoxemia). In cases that do not respond to these measures, pressure breathing has been advocated as a helpful therapeutic measure. It serves to increase slightly the oxygen tension of the inspired air, to combat pulmonary edema, to maintain a more patent lumen during the expiratory phase, and to decrease inspiratory dyspnea. But in status asthmaticus, where the primary difficulty is in expiration (the chest and lungs being already maximally expanded), it would seem that the use of pressure breathing would serve to further the ballooning of the lungs and chest without correcting the main difficulty. Any of these techniques of inhalation therapy will temporarily aid in the effectiveness of breathing and lessen the cyanosis. With intractable bronchial spasm this is accomplished largely by virtue of the active respiratory effort of the patient. The ability to maintain such an expenditure of energy in the face of prolonged anoxemia is obviously limited, and a point is eventually reached where the voluntary musculature becomes quite ineffectual and vital tissues such as the cardiac muscle and brain are dangerously embarrassed by the ever increasing degree of anoxemia. Unless oxygenation can be restored, collapse supervenes and death ensues rapidly.

Since expiration is primarily limited in asthma it would appear that the best procedure for the maintenance of adequate ventilation would be to support this phase. This can be effectively accomplished by the use of the Drinker Respirator which applies positive pressure to the chest wall and abdomen. Since the Respirator also aids inspiration, inspiratory dyspnea is at the same time decreased.



## CASE REPORTS

*Case 1.* R. R., a 45 year old colored female, was brought to the Cincinnati General Hospital in a moribund state on August 19, 1945 at 3 p.m.

The daughter revealed that the patient had been suffering from asthmatic attacks for 8 to 10 years. These episodes had occurred every two to four weeks up until the month prior to admission when they had increased in frequency, and had been occurring every two or three days. Previous attacks had been relieved by adrenalin or by a patent "asthma medicine." The present attack had started about 20 hours before admission to the hospital. Despite the usual medication and two "arm shots" given by her local physician, the patient had become progressively worse and had apparently lost consciousness about five hours before entering the hospital.

On admission the patient was unconscious, deeply cyanotic and in shock. The respirations were feeble and gasping and the respiratory rate was 10 per minute. All the accessory muscles of respiration were in use and the chest position was one of maximal inspiration. The entire chest was hyperresonant. Auscultation revealed only an occasional wheeze, breath sounds were inaudible, and respiratory exchange appeared to be extremely slight. The temperature was 102° F. The pupils were 3 mm. in diameter and did not react to light. The heart sounds were distant and irregular and the pulse was weak. The heart rate was 160 per minute, and the blood pressure was 70/40 mm. Hg. The tendon reflexes were normal throughout; there was no response to plantar stimulation.

Throughout the first 5½ hours of hospitalization 100 per cent oxygen was administered by mask, and the patient was given repeated doses of epinephrine and aminophylline intravenously and intramuscularly, without effect. Two doses of rectal ether were ineffectual. Parenteral fluids were administered intravenously. During the third hour the patient developed paroxysms of fine muscular twitching in the extremities, trunk, and face. The muscular twitching became more marked and at the end of five and one-half hours became convulsive in nature. Respirations were completely ineffectual, and the patient was deeply cyanotic and in shock. The pulse was feeble and irregular.

At this time the patient was placed in a Drinker Respirator. The cyanosis promptly disappeared, the pulse became of good quality, the heart rate fell to 120 per minute and the blood pressure rose. A 20 per cent oxygen-80 per cent helium mixture was substituted intermittently for oxygen. The muscular twitching disappeared. Administration of parenteral fluids (glucose and plasma) was continued. The patient was kept in the Respirator for six hours, and when the Respirator was turned off the patient was able to breathe satisfactorily at a rate of 28 per minute. The breath sounds could now be heard, the expiratory phase being prolonged. There was no wheezing. A few inspiratory râles were heard at both lung bases. Pulse and blood pressure were satisfactory. However, the patient had meanwhile developed a flaccid paralysis of all extremities and tendon reflexes were absent. Despite relief of the respiratory difficulty, the pulse gradually weakened and the blood pressure again fell. The patient was returned to the Drinker Respirator one and one-half hours later but failed to respond to this or to supportive therapy including coramine, caffeine, and plasma, and she died 14 hours after admission. At no time did she regain consciousness.

*Comment.* This patient had been dyspneic for almost a day and was unconscious during the five hours immediately preceding admission. When first examined she showed unmistakable signs of cerebral anoxia, and there followed gradual progression to the point of generalized convulsive mani-

festations before adequate oxygenation was established. The use of the Drinker Respirator afforded immediate and dramatic relief of the anoxemia as evidenced by the disappearance of cyanosis, the improvement in circulation, and the termination of convulsive phenomena. Although the asthma had undergone practically complete remission several hours before death, the patient failed to regain consciousness and there was further progression of the neurological findings. It would appear likely that her death was a direct result of prolonged cerebral anoxia which had initiated irreversible brain damage before adequate therapy could be instituted.

*Case 2.* W. B., a 47 year old white male, was admitted to the Cincinnati General Hospital on March 6, 1946 in a severe attack of acute asthmatic breathing of one hour's duration. His past history revealed onset of bronchial asthma in February 1944. In the following two years he had been seen in the receiving ward on 20 occasions for relief of acute attacks. The duration and frequency of the attacks had steadily increased and the amounts of antispasmodic, sedative, and oxygen therapy necessary for their relief had progressively increased. During this time he had been attending the out-patient dispensary where dental and paranasal foci of infection had been satisfactorily treated; routine medical care had been administered, and desensitization to house dust (the principal allergen revealed by skin testing) had been in progress since June 1944.

On admission the patient was apprehensive and panic stricken. He was deeply cyanotic, his skin was cold, and he was drenched with perspiration. The chest was hyperresonant and fixed in a position of maximum inspiration, with all of the accessory muscles of respiration in use. Respiratory exchange was shallow; loud inspiratory and prolonged expiratory wheezes and rhonchi were heard over the entire chest. The blood pressure was 140 mm. Hg systolic and 100 diastolic and the pulse rate was 120 per minute. The remainder of the physical examination revealed nothing of note.

Oxygen, 100 per cent, by mask, intravenous aminophylline, subcutaneous epinephrine and sodium luminal failed to produce any improvement. After an hour and a half rectal ether was administered, an 80 per cent helium-20 per cent oxygen mixture was substituted for 100 per cent oxygen, and sodium iodide was given by intravenous route. For a while the patient seemed to benefit in that cyanosis was minimal, he seemed more relaxed, and the skin became warmer and less moist; but physical examination failed to reveal any evidence of relaxation of the bronchial spasm. He lost strength rapidly and five hours after admission he was again deeply cyanotic and covered with a cold sweat. Pulmonary ventilation seemed reduced almost to zero and the pulse rate rose to 140 per minute. Collapse seemed imminent. Coramine was given by vein and the patient was placed in a Drinker Respirator.

Improvement was immediate and dramatic. The patient appeared relaxed and comfortable and fell into a restful sleep. His skin became warm and dry and the cyanosis disappeared. The pulse stabilized at 120 per minute and was of good quality. Helium-oxygen mixture was continued throughout by mask and adrenalin in oil was administered at the end of the first hour in the Respirator. The patient remained in the Respirator for nine hours at the end of which time he awakened and was able to breathe adequately without its aid.

Examination now revealed evidence of only a very slight residual amount of respiratory obstruction. Subsequent recovery was uneventful. The patient was discharged from the hospital on March 9, 1946.

*Case 3.* L. G., a 46 year old white male, was brought to the Cincinnati General Hospital in profound shock on October 2, 1946 at 1:59 a.m. History revealed that

the patient had been suffering from asthma for six years. Attacks had been occurring more frequently during the preceding months, and for the five days prior to admission the patient had been unable to sleep at all because of difficult breathing. He had been using an adrenalin spray with some relief but on September 30, 1946 he had been obliged to call his local physician who administered adrenalin in oil and penicillin. Adrenalin in oil was given twice the following day (October 1) but dyspnea became progressively worse and patient was brought to the hospital early the next morning.

On admission the patient was cyanotic with cold clammy skin, unobtainable blood pressure, and a pulse rate of 150 per minute. The chest was emphysematous and fixed in the position of maximum inspiration. He was extremely apprehensive and restless; respirations were rapid (42 per minute) and extremely shallow. The breath sounds were almost inaudible on auscultation. The neck veins were distended; there was no peripheral edema. The temperature was 97° F. The white blood count was 17,500 white cells per cu. mm. with 85 per cent polymorphonuclear leukocytes and 15 per cent lymphocytes.

For the first five hour period 100 per cent oxygen was administered by mask. During this time the patient was given repeated intravenous injections of aminophylline, two six ounce doses of rectal ether, sodium iodide intravenously, epinephrine by subcutaneous injection, physiologic saline solution and plasma by vein, plus 100 mg. of Demerol and 4 grains of sodium amytal intramuscularly. Despite the therapy listed above no improvement was noted in the breathing or cyanosis, and the patient continued to be very restless and anxious. The blood pressure was still unobtainable.

At 7:00 a.m. an endotracheal tube was inserted and an 80 per cent helium-20 per cent oxygen mixture was substituted for 100 per cent oxygen, without effect. The temperature rose abruptly to 100° (rectal). Penicillin, 20,000 units, was injected intramuscularly and repeated every three hours thereafter. At 9:00 a.m. (seven hours after admission) the patient was placed in the Drinker Respirator. An additional 7½ grains of sodium amytal (intramuscularly) was required to quiet the patient sufficiently to allow for synchronization of his respirations with the rhythm of the Respirator. As soon as this had been accomplished there was dramatic disappearance of the cyanosis and recovery from the state of shock. The blood pressure was obtainable at 125/70 mm. Hg and the pulse slowed to a rate ranging between 90 and 120 per minute. For the first six hours in the Respirator this improvement in the patient's condition was maintained. Expiration remained prolonged but the breath sounds were clearly audible and the wheezes disappeared. Circulation remained adequate, and the color of the skin and mucous membranes indicated satisfactory oxygenation. During this period the patient received additional parenteral fluids, sedation as needed, and frequent intravenous injections of epinephrine.

At 4:00 p.m. temperature rose to 106.2° (rectal) and moderate cyanosis reappeared. Numerous fine inspiratory râles, rhonchi and occasional expiratory wheezes could be heard in the chest. Subsequently, his course was rapidly and progressively downward. At no time was he able to breathe adequately without the support of the Respirator, although bronchial spasm seemed minimal on physical examination. Twenty-two hours after admission the patient died.

*Comment.* The development of high fever, râles, and polymorphonuclear leukocytosis in this case is felt to indicate the presence of a complicating bronchopneumonia. The patient had suffered from prolonged respiratory distress for five days before admission to the hospital, and for the last two days of this period he had been severely dyspneic. Nevertheless, under treatment with the Drinker Respirator, there was prompt and main-

tained relief of the anoxemia, shock, and obstructive dyspnea before pneumonia altered the course of events.

### DISCUSSION

In all three cases under consideration the specific and directed application of mechanical energy for the support of expiration appears to have furnished the necessary crutch for maintenance of adequate respiratory exchange until the bronchial spasm had undergone remission. Disappearance of cyanosis was prompt and dramatic in each of these patients. In addition, improvement in the circulation attendant on the relief of anoxia is evident in each of the records. The recovery from shock in Case 3 after establishment of adequate oxygenation is particularly notable, and emphasizes the important rôle of oxygen in the treatment of shock. The unfavorable outcomes in Cases 1 and 3 can be explained on the basis of complicating factors, and need not be regarded as indicating failure of the therapy under consideration. The second patient was treated early in the course of his attack and recovered uneventfully. It is quite possible that if therapy could have been instituted earlier in Cases 1 and 3 the final outcomes would have been more favorable.

### COMMENT

It is at once apparent that the induction of partial anesthesia is an integral part of the treatment. A patient in acute respiratory distress, being anxious and fearful to the point of panic, will attempt to fight the machine and be made worse unless the level of consciousness is sufficiently depressed to permit passive acceptance of the mechanical aid. Eighty per cent to 90 per cent synchrony of the excursions of the machine with the patient's respirations will provide adequate oxygenation. Adjustments in the rate or the pressure, or both, may be required as the treatment progresses.

### SUMMARY AND CONCLUSIONS

The use of anesthesia plus the Drinker Respirator for artificial respiration, with active support of expiration, is suggested as an additional tool in the armamentarium of therapy for acute status asthmaticus. The pathological physiology of acute intractable asthma is discussed in relation to the rationale of this form of treatment. Three cases treated in this manner are presented and in each, prompt and satisfactory relief of anoxemia was accomplished and maintained until bronchiolar spasm had undergone remission. While it is admittedly impossible to draw any conclusions from limited experience such as this, we feel that the rationale is sufficiently clear and the results insofar as relief of anoxemia is concerned, are gratifying enough to warrant its use in refractory status asthmaticus. From our experience it is felt that it is of utmost importance that the therapy be instituted early in the course, before irreversible changes have appeared, or other grave

complications have had time to gain foothold. This maneuver is not suggested as a substitute for other well-established methods of treatment, but rather as an adjunct to them in refractory cases.

#### BIBLIOGRAPHY

1. UNGER, L.: *Bronchial asthma*, 1945, Chas. C. Thomas, Springfield, Ill.
2. FRENCH, M., and ALEXANDER, F.: Psychogenic factors in bronchial asthma, *Psychosomatic Medicine Monographs*, II, 1939 and IV, 1941.
3. BARACH, A. L.: The treatment of bronchial asthma and other chronic pulmonary diseases accompanied by constriction in the bronchial passageway, *Med. Clin. N. Am.*, 1944, 339.
4. BEST, C. H., and TAYLOR, N. B.: *The physiological basis of medical practice*, Second Edition, 1940, The Williams and Wilkins Company, Baltimore, Md., p. 496.
5. WILSON, J. L., and FINDLEY, T.: Obstructive pulmonary emphysema, *Med. Clin. N. Am.*, March 1944, 356.
6. PRINZMETAL, M.: The relation of inspiratory distention of the lungs to emphysema, *Jr. Allergy*, 1934, v, 493.

# TREATMENT OF CARDIOVASCULAR SYPHILIS \*

By H. EISENBERG, M.D.,† *Chicago, Illinois*

## INTRODUCTION

CARDIOVASCULAR syphilis is frequently a problem to the internist. Ten to 15 per cent of cases of recognized cardiovascular disease, Blumgart <sup>1</sup> has estimated, are due to syphilis. Statistical studies by Moore <sup>2</sup> and by Leiby and Callaway and their coworkers <sup>3</sup> indicate that there are approximately 240,000 patients with syphilitic cardiovascular disease in this country at any one time and between 20 and 30 thousand die annually from it. Since the time of Ehrlich, the treatment of this disease has been a controversial matter, and remains so today notwithstanding the widespread and effective use of penicillin in therapy of early syphilis. Before discussing treatment, a brief review of the morbid anatomy and clinical signs of the disease is indicated.

Syphilis may appropriately be considered a general systemic infection with *Treponema pallidum*, in the course of which local lesions may occur, early or late, which may be striking enough to attract clinical attention. The most characteristic and widespread histologic changes, consequent to invasion by the spirochetes, consist of mononuclear cell infiltration in the perivascular lymph spaces. According to Longcope,<sup>4</sup> such changes may occur in the aorta during the secondary stage, concomitantly with the cutaneous manifestations. In cases of late syphilis at necropsy, Warthin<sup>5</sup> reported that 70 to 90 per cent showed histologic evidence of cardiovascular involvement. The high incidence of cardiovascular lesions in late syphilis, often clinically unrecognized, has been confirmed by postmortem studies made by Langer<sup>6</sup> and by Stokes<sup>7</sup>—Langer on over 23,000 autopsies. Antemortem clinical evidence of syphilitic cardiovascular disease existed in 39.5 per cent of Langer's cases, in 43 per cent of those reported by Lucké and Rea<sup>8</sup>; and in 16.2 per cent of a group of necropsy reports reviewed by Moore and his group.<sup>9</sup>

Clinical studies similarly reflect the incidence of clinically recognizable cardiovascular disease in late syphilis. Bruusgaard<sup>10</sup> estimated that 10 per cent of untreated cases of late syphilis, studied serologically and clinically, had clinically recognizable evidence of cardiovascular disease. In a group of 6,253 patients with late syphilis, either under observation or treatment for six months or longer by the Cooperative Clinical Group,<sup>11</sup> a clinical diagnosis of cardiovascular disease was made in 9.9 per cent. Turner's<sup>12</sup> study

\* Read at the postgraduate course on cardiovascular disease, Northwestern University Medical School, Chicago, Illinois, as arranged by the American College of Physicians, April 23, 1947.

† Surgeon (R), U. S. Public Health Service.

Under the direction of Herman N. Bundesen, Senior Surgeon (R) (Inactive), U. S. Public Health Service; President, Chicago Board of Health.

of over 6,400 untreated cases of late syphilis showed an incidence of about 10 per cent; diagnosis of uncomplicated aortitis was made in 5.3 per cent, aneurysm in 1.2 per cent, and aortic insufficiency in 2.7 per cent.

Clinically significant pathologic changes appear to be restricted to the aorta and coronary ostia. In the aorta, early perivascular inflammatory reaction results in destruction of the elastic fibers of the media and consequent loss of resiliency. When this occurs in the aortic ring, dilatation of the ring with separation of the valve cusps occurs, followed by valvular incompetence. The same process of elastic tissue destruction and dilatation may involve the aorta diffusely. Diffuse aortitis is the most common and earliest form of syphilitic cardiovascular disease, located primarily supra-valvular. When mesaortitis and dilatation are relatively localized, aneurysm results. A fourth type of cardiovascular involvement is consequent to intimal swelling about the coronary ostia. Carr<sup>13</sup> has estimated that less than 10 per cent of cases with aortic syphilis show clinical or electrocardiographic evidence of coronary involvement.

It might be well at this time to relate the anatomic changes just outlined to clinical signs commonly observed in cardiovascular syphilis. That these may occur early is attested by Brooks,<sup>14</sup> who has observed that cardiac arrhythmias, aortitis, and myocarditis frequently occur in secondary syphilis but will soon disappear if the case is given vigorous antisyphilitic therapy. Longcope<sup>4</sup> noted that clinically recognizable syphilitic aortitis may occur within a few months after primary infection, although the process is usually latent for longer intervals, up to 10 or more years.

Uncomplicated aortitis affecting the supra-valvular region, with or without slight dilatation, is the most common and earliest cardiovascular change in syphilis.

This specific involvement will give rise to a characteristic physical sign—accentuation of the aortic second sound, described as tympanitic, drum-like, or of tambour quality—due to altered physical characteristics. This early clinical sign is usually accompanied by another just as characteristic, reflecting altered hemo-dynamics—a systolic murmur over the aortic area.

Cole, Usilton and their associates,<sup>11</sup> who reviewed material of the Co-operative Clinical Group, as well as Stokes,<sup>15</sup> consider a retrosternal pain of burning quality and typically unrelated to exertion as a characteristic symptom of uncomplicated aortitis. On the basis of experience at the Chicago Municipal Social Hygiene Clinics and at the cardiovascular disease clinic at Beekman Hospital in New York, we concur with the views of Dressler,<sup>16</sup> Maynard,<sup>17</sup> and Wilson<sup>18</sup> that the presence of this symptom is indicative of progression and of complication of the aortitis. The same can be said for coronary paroxysmal pain with characteristic radiation of angina-like attacks as well as of paroxysmal dyspnea, particularly nocturnal attacks. These physical signs relate to involvement of the coronary ostia, not to the coronary arteries themselves. In many of these cases one will find changes in the

electrocardiogram. They resemble those seen in coronary heart diseases, like chronic coronary insufficiency of the progressive type. Frequently, left ventricular failure follows, indicating a progressive cardio-aortic process.

The earliest detection of the aortic dilatation depends upon roentgen-ray examination, which is of particular value in patients less than 40 years of age without hypertension or other cardiac pathology. Fluoroscopic and roentgenographic examination should be made in all cases of late syphilis before diagnosis is completed. More advanced dilatation may manifest itself in classic supra-cardiac dullness or by causing suprasternal pulsation so that existing aneurysm may be suspected.

Aneurysm may be diffuse or saccular; the latter, when it occurs, is always of syphilitic origin. Diagnosis of this lesion depends upon both clinical and roentgenologic evidence.

The high degree of coexistence of cardiovascular and neurologic lesions in late syphilis is worth noting. It was found that neurosyphilis was present in 54 per cent of cardiovascular syphilitic cases studied at the Mayo Clinic,<sup>29</sup> and in 49 per cent of 6,253 cases collected by the Coöperative Clinical Group. Cases of neurosyphilis should, therefore, be carefully screened for cardiovascular lesions before treatment is undertaken.

A further progression of the syphilitic process may cause valvular incompetency with characteristic signs of a diastolic murmur over the aortic region of the heart with cardiac enlargement and high systolic with low diastolic blood pressure reading, followed by signs of congestive heart failure.

Early case-finding, adequate treatment, and systematic post-treatment observation of early syphilis is the most effective means of preventing cardiovascular syphilis. The increasingly wide application of more effective treatment since Ehrlich's introduction of arsenotherapy in 1910 appears, in the opinion of Thompson<sup>20</sup> and others, to be reflected in a decreasing prevalence of syphilitic cardiovascular disease during the last two to three decades—an opinion expressed also by pathologists.<sup>21</sup>

It seems reasonable that since penicillin has been used in syphilis, a large number of patients have probably been treated inadequately; many of those may have disappeared from observation and possibly will not come under medical observation again before they show late signs of syphilis, and particularly, cardiovascular syphilis. An even greater menace exists in the fact that oral penicillin preparations have become available and may be used for self-medication. Because this drug in relatively small doses may cause remission of cutaneous lesions without in any sense arresting the disease, there is good reason to expect that disastrous results may come to the attention of internists and cardiologists within a few years.

Without further dwelling upon the importance of the underlying syphilitic pathology and symptomatology and the relationship of these two in order to arrive at a correct diagnosis and raise the index of suspicion, let us now consider the application of chemotherapy to the treatment of syphilitic cardio-



vascular disease. Reported experience with penicillin is limited. It appears, however, that considerations applying to conventional therapy with arsenic and bismuth preparations are valid for penicillin as well.

### THERAPY WITH METALLIC COMPOUNDS

Soon after the introduction of salvarsan, fatalities during the course of treatment in early and late syphilis were observed. These were attributed to myocardial damage or to ventricular fibrillation, due to the higher toxicity of the older drugs. This was substantiated by the investigations made by Reid,<sup>22</sup> who found that the arsenicals decrease the rate of conduction in the heart and shorten the refractory period in the heart muscle.

It was also observed that the phenomenon of therapeutic shock, or the Herxheimer reaction, might be implicated in the etiology of occlusion of the coronary ostia, aneurysmal rupture, or abrupt cardiac decompensation. The Herxheimer reaction may be characterized as a transient exacerbation of the local lesions of syphilis as an early response to treatment. It has been discovered empirically that this phenomenon may be minimized by the induction of therapy with small, but constantly increasing, doses. Another potential hazard of treatment in cardiovascular syphilis is the so-called therapeutic paradox, to which attention has been directed by Wile.<sup>23</sup> In this state, the too-rapid healing of syphilitic lesions with consequent scar-tissue formation may result in anatomic healing but functional deterioration. Sudden encroachment on the coronary orifices during therapy presents particular risk in this connection.

Because of early unfavorable results, arsenotherapy fell into relative disrepute until the introduction of less toxic compounds, notably neoarsphenamine and the even less toxic oxophenarsine hydrochloride, which appeared on the market under the proprietary name of Mapharsen.

The scheme of treatment should depend upon the anatomical diagnosis and functional state of the patient. In the presence of uncomplicated aortitis, conventional therapy with alternating courses of arsenical and bismuth compound may be recommended. The first course may be one of the arsenicals, administered at weekly intervals and beginning with small but increasing amounts. At the Municipal Social Hygiene Clinic, oxophenarsine is being employed in an initial dose of 0.03 gram, increasing at weekly intervals to 0.06 gram, with weekly injections of insoluble bismuth 0.2 gram given at the same time. Bismuth may also be given alternately between courses of eight weekly arsenicals for 10 weeks, the treatment to last from 9 to 12 months, giving about 24 arsenicals and 40 bismuth injections. Untoward effects and severe Herxheimer reactions are uncommon in uncomplicated aortitis. Schottmuller<sup>24</sup> and others have also given the arsenicals without preliminary preparation with bismuth or other anti-syphilitic drugs without harmful effects. To begin with the arsenicals in this form of aortic syphilis is contrary to the Moore<sup>25</sup> and the Johns Hopkins School of Medicine, which

advocated preparatory heavy metal for a period of 12 weeks, to be followed by the arsenicals in gradual increasing doses. It is important to note that the stage of uncomplicated aortitis is the most favorable time for treatment. Progression may be arrested by adequate therapy; and dangerous complications of treatment are minimal.

In the presence of aneurysm, valvular lesions, or electrocardiographic evidence of coronary damage, the induction of therapy must be much more gradual. Bismuth should be administered at weekly intervals for at least three months prior to the use of arsenicals. At the discretion of the therapist, bismuth may be preceded by or supplemented with appropriate, graduated doses of potassium iodide. In the absence of reactions and the presence of adequate cardiac reserve at the end of such a period of preliminary therapy, an arsenical compound may be begun in graduated doses in the manner described before. It might be well to state here that patients with complaints of substernal pain, treated in this manner, will usually feel remarkably improved physically and their symptoms may disappear completely.

If there is a history of cardiac decompensation, or if congestive failure has occurred prior to or during the course of specific syphilotherapy, specific chemotherapy should be abandoned entirely or not begun until adequate cardiac reserve has been reestablished by customary methods of treatment such as digitalis, diuretics, and bed rest. Impaired renal function consequent to decreased circulatory efficiency is a distinct contraindication to the use of compounds as toxic as those containing arsenic or bismuth. And in the presence of circulatory failure, exposure of a critically impaired cardiovascular system to the added hazard of Herxheimer reaction or therapeutic paradox cannot be justified, whether as a consequence of arsenicals or of penicillin therapy.

Experience of the coöperative clinics, as reported by the Committee on Medical Research and the U. S. Public Health Service<sup>26</sup> concerning treatment of early syphilis with penicillin, indicates that the incidence of febrile Herxheimer reactions is high with this drug. Moore,<sup>27</sup> summarizing experience at the Johns Hopkins Hospital and elsewhere, recommends the following schedule of penicillin therapy for cardiovascular syphilis: aqueous solutions of penicillin are administered intramuscularly at three-hour intervals. During the first day, the individual dose is limited to 1,000 units; during the second, increased to 5,000 units; next day to 10,000 units; 25,000 on the fourth and a standard individual dose level of 50,000 units on the fifth day, which is maintained until the twenty-second day to a total of 8.9 million units. No instances of therapeutic shock were observed in a group of 12 cases of aortic regurgitation, aneurysm, or syphilitic aortitis with coronary ostial stenosis and angina of effort, which he treated by this program. One patient with coexistent paresis died on the fourth day, presumably from heart failure. The aorta showed plaques of syphilitic aortitis, each containing a

large fresh hemorrhage. No other patient was worse after therapy. In Moore's cases, the serologic response was, like that of late syphilis, in general, inappreciable.

Russek,<sup>28</sup> at U. S. Marine Hospital in Staten Island, used doses of 40,000 units every two hours for 85 doses, in 15 cases of aortitis and aneurysm, without any undue reactions.

Dolkart and Schwemlein<sup>29</sup> undertook treatment of two patients with aortic insufficiency, one of whom had associated rheumatic heart disease, frequent anginal attacks, and several previous episodes of congestive failure. Treatment was discontinued because of the development of fresh anginal attacks, and ventricular extrasystoles, in the first case. The second patient developed intermittent precordial distress after four days and was given no more therapy.

The experience of Peters<sup>30</sup> at the Intensive Treatment Center of the Chicago Health Department, and our own experience at the Municipal Social Hygiene Clinic, have been quite favorable. At the Chicago Intensive Treatment Center, 20 cases of neurosyphilis with coexisting cardiovascular involvement have been treated with several programs of aqueous penicillin. Some cases were started with 5,000 units; the dose was gradually increased to 10,000, 20,000, 30,000 and 40,000 units every three hours up to a total of 6,000,000 units. Other cases were given 40,000 units every three hours, for a total of 2,400,000 units, with few complications.

At the Municipal Social Hygiene Clinic, about 20 patients with uncomplicated aortitis have been treated with penicillin in the oil and beeswax vehicle devised by Romansky. An initial dose of 100,000 units in one injection is given, and increased by 100,000 units after the third and fifth day to 300,000 units to a total of 4,500,000 units in 15 to 20 days. We have observed no untoward reaction. No data on extended observation after treatment are available as yet; the longest period during which any of our patients has been observed is four months. Final time-dose relationship has not as yet been established. Wile,<sup>32</sup> writing in the Rapid Treatment Center bulletin, again has cautioned us against too intensive methods in the treatment of cardiovascular syphilis. After the disease has reached a clinical horizon, treatment reactions are more apt to occur. This relates to either the arsenicals or penicillin, both of which are fast-acting drugs.

### CONCLUSION

In conclusion, early case-finding, adequate treatment, and careful observation of early syphilis are important in prevention of late cardiovascular disease. Selection of treatment in the late case depends upon accurate diagnosis of anatomic changes and evaluation of functional reserve. Uncomplicated aortitis and some cases of aneurysm may be treated with low risk and reasonable expectation of success with conventional alternating courses of arsenic and bismuth compounds. In the presence of valvular disease,

aneurysm or history of congestive failure, treatment must be initiated with bismuth for two to three months, followed by gradually increased doses of an arsenical compound. In all cases, initial doses must be graded to minimize the risk of severe Herxheimer reactions. In the presence of decompensation and until the establishment of adequate cardiac reserve by conventional means, no form of syphilotherapy should be employed. After establishment of cardiac compensation, gradually increased doses of bismuth should be given for at least three months, followed by weekly injections of 0.005 gm. of mapharsen, increasing to 0.03 gm. In cases of repeated congestive failure or myocardial and coronary involvement, as evidenced by electrocardiographic records, only mercury or bismuth is indicated—never any arsenicals. Evidence from records of the Chicago Board of Health, Johns Hopkins Hospital and Staten Island Marine Hospital indicates that penicillin begun with graded doses may be used in uncomplicated aortitis and aneurysm with acceptably low risk. More complete evaluation of penicillin in syphilitic cardiovascular syphilis cannot be made at present.

## BIBLIOGRAPHY

1. BLUMGART, H. L.: Detection and treatment of cardiovascular syphilis, *New England Jr. Med.*, 1940, ccxxiii, 443.
2. MOORE, J. E., DANGLADE, J. H., and REISINGER, J. C.: Diagnosis of syphilitic aortitis uncomplicated by aortic regurgitation of aneurysm, *Arch. Int. Med.*, 1932, xlix, 753.
3. LEIBY, G. M., CALLAWAY, J. L., and FLEMING, W. L.: Diagnosis and management of asymptomatic uncomplicated aortitis, *North Carolina Med. Jr.*, 1940, i, 301.
4. LONGCOPE, W. T.: Syphilitic aortitis, its diagnosis and treatment, *Arch. Int. Med.*, 1913, xi, 15.
5. WARTHIN, A. S.: The lesions of latent syphilis, *Southern Med. Jr.*, 1931, xxiv, 273.
6. LANGER, E.: Die Häufigkeit der luetischen Organveränderungen, insbesondere der Aortitis luetica, *Munchen. med. Wchnschr.*, 1926, lxxiii, 1782.
7. STOKES, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 900.
8. LUCKÉ, B., and REA, E.: in STOKES, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 896.
9. MOORE, J. E.: See reference 2 above.
10. BRUUSGAARD, E.: Summary of Bruusgaard's data as to ultimate outcome of untreated syphilis. From MOORE, J. E.: Modern treatment of syphilis, 1943, Charles C. Thomas, Springfield, Ill., p. 38.
11. COLE, H. N., and USILTON, L. J.: Cooperative clinical group; studies in the treatment of syphilis, *Ven. Dis. Inform.*, 1936, xvii, 95.
12. TURNER, T. B.: In STOKES, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 896.
13. CARR, J. G.: The gross pathology of the heart in cardiovascular syphilis, *Am. Heart Jr.*, 1930, vi, 30.
14. BROOKS, H.: The treatment of cardiovascular syphilis, Warthin Anniversary Volume, Wehr, Ann Arbor, 1927, p. 117.
15. STOKES, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 907.
16. DRESSLER, M.: Cardiovascular syphilis; an approach to early clinical recognition and early treatment, *Conn. State Med. Jr.*, 1945, ix, 848.

17. MAYNARD, E. P., JR.: Diagnosis of cardiovascular syphilis, *Brooklyn Hosp. Jr.*, 1940, ii, 69.
18. WILSON, R., JR.: Studies in syphilitic cardiovascular disease. I. Uncomplicated syphilitic aortitis; an asymptomatic condition, *Am. Jr. Med. Sci.*, 1937, cxciv, 178.
19. MAYO CLINIC: *In* STOKES, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 931.
20. THOMPSON, W. P., CORNEAU, W. J., and WHITE, P. D.: The role of the treatment of syphilis in the prevention of cardiovascular involvement, *Am. Heart Jr.*, 1939, xvii, 286.
21. Private communication to author.
22. REID, W. D.: The mechanism of the toxic action of arsphenamine on the heart, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 883.
23. WILE, U. J.: The treatment of the syphilitic liver and heart, a therapeutic paradox, *Am. Jr. Med. Sci.*, 1922, clxiv, 415.
24. SCHOTTMULLER, H.: On the treatment of syphilis of the aorta, *Am. Jr. Syph.*, 1925, ix, 1.
25. MOORE, J. E.: The modern treatment of syphilis, 1943, Charles C. Thomas, Springfield, Illinois, p. 294.
26. Committee on Medical Research and the U. S. Public Health Service: The treatment of early syphilis with penicillin, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 265.
27. MOORE, J. E.: Penicillin in syphilis, 1947, Charles C. Thomas, Springfield, Illinois, p. 195.
28. RUSSEK, H. I., CUTLER, J. C., FROMER, S. A., and ZOHMAN, B. L.: Treatment of cardiovascular syphilis with penicillin, *Ann. Int. Med.*, 1946, xxv, 957-959.
29. DOLKART, R. L., and SCHWEMLEIN, G. X.: The treatment of cardiovascular syphilis with penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 515-516.
30. Private communication from E. E. Peters to author.
31. To be published.
32. WILE, U. J.: Cardiovascular syphilis, *Rapid Treatment Center Bulletins*, 1945, ii, 12.

# MANAGEMENT OF DIABETES MELLITUS: AN ANALYSIS OF PRESENT-DAY METHODS OF TREATMENT \*

By HERMAN O. MOSENTHAL, M.D., F.A.C.P., *New York, N. Y.*

A COMPLETE life span, full activities and freedom from any physical or mental impairments are possible for the diabetic today. All diabetics do not reach this goal, but many of them do. The problem before us is: how should we manage diabetics to keep them in normal health?

Mass control, statistical evaluations and their mechanical interpretations have set the pace for a regimented therapy of a number of diseases. Diabetes and hypertension have been particular victims of this method of approach. Both patients and doctors are under pressure to enforce one or the other rigid system of treatment for all diabetics without regard to their personality or the type of diabetes involved. Such one-track methods of diabetes control have been advocated by individual physicians and some medical groups. Life insurance acceptability, from the company's point of view, may be judged adequately from a collection of 5,000 cases. However, there is no safety or satisfaction for those diabetics who suffer harm because their particular case does not fit the plan prescribed by their medical adviser.

There are three sects endorsing special systems of diabetes management. I am naming them according to informal, frequently used terms:

1. Purists
2. Middle of the Roaders
3. Free Dieters

The diabetic state of any patient may change from month to month, or year to year, and a form of treatment which is beneficial at one time, may be distinctly harmful at another. No single system of diabetes control meets all situations at all times; diabetes is not a disease of unitarian etiology, nor of predictable development.

The basic principles of the three sects advocating fixed procedures for diabetes therapy are shown in table 1. Diet, blood sugar and glycosuria are the three pivotal expedients by which diabetes control is accomplished. These will be taken up separately and the ideas concerning them can be applied to the requirements of each patient. This method of analysis encourages greater freedom of action by the physician and more rational application of therapy than if all three clinical yardsticks were rigidly fixed and delivered in a sealed container like army rations.

\* Read at the New England Postgraduate Assembly, October 30, 1947.

TABLE I

Basic Principles of the Three Sects Advocating Fixed Procedures for Diabetes Therapy

	Diet	Blood Sugar	Glycosuria	Special Notes
Purists	No sugar, meticulously calculated and measured, adequate for maintenance	Normal level constantly maintained	Completely checked	Some regard this as a temporary measure to aid recuperation of the islet cells; others insist on it as a permanent plan
Middle of the Roaders	No sugar, about 150 gm. carbohydrate, adequate protein	Normal level as far as possible, at least at intervals during the day	Most specimens sugar free, some may at times contain sugar, no more than 10-20 gm. in 24 hours.	Avoid hypoglycemic reactions
	High carbohydrate, no sugar, low fat			
Free Dieters	Carbohydrates, including sugar, as desired	Blood sugar level disregarded	Glycosuria disregarded	Protamine zinc insulin once a day; no other form of insulin

## DIET—FOODS AND THEIR USE IN DIABETES

*Caloric Requirements.* Suitability of the caloric intake must be judged by the weight of the patient. Fewer calories than those deemed requisite on scientific grounds are nearly always sufficient. The details are given in table 2. Leanness in all human beings is conducive to longevity and in addition it offers the diabetic the possibility of amelioration of his disease.<sup>1</sup>

TABLE II

## Caloric Requirements

*Recommended daily caloric intake* by the Committee on Foods and Nutrition, National Research Council

	Man (70 Kg.)(154 lbs.)	Woman (56 Kg.)(123 lbs.)
Sedentary	2500	2100
Moderately active	3000	2500
Very active	4500	3000

*In practice caloric requirement* should be judged according to weight control (quantitative nutrition). Average caloric needs have been found to be:

Men—city dwellers—executives, doctors, bus drivers, etc.

1800 to 2100 calories

Women—housewives, clerical workers, etc.

1500 to 1800 calories

Growing children

Hard manual workers } much higher calories are essential.

*Carbohydrates.* Sugar (or sugar-containing foods) should be avoided since their ingestion results in an explosive rise of blood sugar that puts a fluctuating strain upon carbohydrate metabolism to which the diabetic does not respond, either with or without insulin. For psychological adjustments, especially in children, desserts or soft drinks may, on occasion, be substituted

for the equivalent of starchy food in the diet, or compensated for by supplementary doses of insulin. Sugar may be eaten by some diabetics without producing glycosuria or hyperglycemia while they are receiving no insulin or only small doses. There is no reason why they should not receive sugar. However, such cases are very rare and it is a matter of trial and error to ferret out these patients.

A diet satisfactory for an indefinite period may be provided by a daily intake of 150 grams of starch. This amount allows for one slice of bread for each of four meals, one helping of the starchy, 20 per cent vegetables, e.g. potato, rice, macaroni; one glass of milk; a helping of the 10 per cent vegetables, onions, carrots, beets, etc., and two helpings of the 10 per cent fruits, e.g. oranges, grapefruit, besides the 3 per cent vegetables and the foods containing protein and fat only. Such a diet may be regarded as a normal carbohydrate diet.

High carbohydrate diets containing 250 to 300 grams of carbohydrate, as advocated by some clinicians, for universal use in diabetes, undoubtedly are applicable to growing children and those engaging in hard manual labor. However, in most adults such diets tend to result in obesity and their control by insulin is more difficult than with a lower starch intake.

The variable amount and kind of carbohydrate consumed on the free diet regime make it impossible to control glycosuria and it is only if unlimited urinary sugar is to be sanctioned that such a procedure can be endorsed.

TABLE III

## Carbohydrates in the Diabetes Diet

*Sugar* and sugar containing foods to be avoided, except for psychological adjustments, particularly in children.

*Carbohydrate 150 gm.* provides an ample and palatable diet for continued use.

*Carbohydrate 200 to 300 gm.* is usually more than most persons desire to eat. It is advocated for routine use in the so-called high carbohydrate diets. Glycosuria on such diets is as a rule difficult to control. High carbohydrate diets are applicable to growing children, athletes and hard manual laborers, but not to sedentary persons or those taking moderate exercise.

*Free diets* sanctioning variable amounts of all kinds of carbohydrate make it difficult, practically impossible, to keep glycosuria within reasonable bounds.

*Proteins.* The integrity of the body depends upon an adequate assimilation of proteins. The belief that proteins, especially meats, and particularly red meats, tend to elevate blood pressure and are a cause for arteriosclerosis, has been proved erroneous. A diet deficient in protein results in degenerative changes in the kidneys and presumably other tissues,<sup>2</sup> in anemia and in hypoproteinemia. Degenerative lesions of arteries precede the deposit of cholesterol in the production of arteriosclerosis and it is possible that insufficient protein may be partly responsible for the more frequent presence of arteriosclerosis in diabetics than in normal persons. Protein deficiency may have a dual origin in the diabetic, through a scant intake and because of insufficient insulin. Consequently not only the amount of protein eaten, but also the necessary insulin coverage demand attention for the conservation of body tissues. It has been shown that protamine zinc insulin brings about



far better results in pulmonary tuberculosis complicating diabetes than does unmodified insulin.<sup>3</sup> The reason for this is that each dose of unmodified insulin checks protein destruction and loss for four hours only, whereas every injection of protamine zinc insulin accomplishes this for 24 hours.<sup>4</sup>

Recently the deficiency of serum proteins has been stressed as an accompaniment of and as a cause of the much dreaded diabetic retinopathy.<sup>5</sup> For the maintenance of health and strength and for the prevention of many of the complications of diabetes the preservation of the body proteins is of great importance. The protein intake should exceed rather than be less than the traditional gram per kilo and should include animal proteins in liberal amounts. The diet slogan: meat, fish or eggs at each meal, has decided merits. It is well known that marked glycosuria is accompanied by protein destruction. This can and should be checked by insulin administration effective throughout the 24 hours.

TABLE IV

## Proteins in the Diabetes Diet—Qualitative Nutrition

When nutrition or maintenance is considered body weight is always the lay criterion and often the medical standard. However, there are two kinds of nutrition, quantitative, which is of little value, and qualitative, which is essential.

*Quantitative nutrition* is the accumulation of fat.

*Qualitative nutrition* depends on effectual protein integration.

It is judged by hemoglobin, red blood cell count and level of serum proteins.

It is maintained by an ample protein intake, including meats, 75 to 120 gm. per day.

In diabetes prevention of inordinate glycosuria and adequate insulin dosage check protein destruction.

Good qualitative nutrition favors the healing of infections, e.g. tuberculosis, and will do much to prevent the dreaded present day complications of diabetes: arteriosclerosis, nephritis and retinopathy.

*Fats.* The use of fats in the diabetes diet has been decried with excessive vehemence. The minimum carbohydrate and protein, but extremely high fat diets as originally advocated by von Noorden and later by Newburgh, are at present endorsed by no one. A high fat intake is accredited with diminishing carbohydrate tolerance and with the production of arteriosclerosis. Both of these drawbacks deserve consideration. On the other hand, a certain amount of fat is a necessary nutrient. The provision of fat soluble vitamins and of calcium can be accomplished only by certain fatty foods. In antiobesity diets it has been found advisable to prescribe a minimum of one egg and a glass and a half of milk a day. The diabetic, except when calories are restricted because of obesity, may have more of these and the addition of some butter and cheese is desirable. The adjustment of the fat intake in the usual restricted carbohydrate diets of diabetes is the obvious means of weight regulation, unless the amount of alcohol consumed is a factor.

*Alcohol.* Alcohol is a valuable form of food in diabetes. It is a good source of calories; it does not form sugar; it has so-called anti-ketogenic properties. The alcoholic beverages containing sugar, especially beer, champagne and cocktails, should be avoided, while whiskey, brandy, dry wines

and others free of sugar may be taken as desired. The control of loss or gain of weight by the regulation of alcohol is self-evident.

TABLE V

## Fats and Alcohol in the Diabetes Diet

*Fats*

High fat intake reduces glucose tolerance and produces arteriosclerosis.  
Some fat is required for the provision of fat soluble vitamins and calcium.  
Minimal of fatty foods is: 1 egg and  $1\frac{1}{2}$  glasses of milk a day.  
More of these as well as butter and cheese are advisable.  
In the diabetic, adjustment of the fat intake serves to regulate weight.

*Alcohol*

Sugar-containing alcoholic beverages—beer, champagne, cocktails, are forbidden.  
Whiskey, brandy, dry wines may be taken.  
Alcohol is a good source of calories, does not form sugar and has anti-ketogenic properties.  
Weight control by prescribing or withholding alcohol should be considered.

## BLOOD SUGAR

Some plans of diabetes management call for a blood sugar always at normal levels, others allow intermittent hyperglycemia, while the free diet school pays little or no attention to the sugar in the blood. From the many clinical and experimental observations it appears that each of these proposals is applicable in certain types of diabetes.

A low blood sugar persistently maintained will promote the healing of hydropic lesions in the pancreatic islets.<sup>6</sup> It is thus shown that hydropic degeneration is reversible. Little is known about the occurrence of such changes in the human pancreas. However, the rehabilitation of the pancreatic function in diabetes of recent origin whether in children,<sup>7</sup> the obese<sup>8</sup> or after a particular insult, e.g. an acute infection, points to a restoration of the beta cells in the islands of Langerhans. Such types of diabetes should be accorded the most painstaking care and a normal blood sugar should be maintained in them for a period of weeks after the insulin requirement has ceased to diminish or the tolerance to ingested carbohydrates no longer increases. When the insulin need is less than 30 units, a purist objective should be continued for reasons given in the next paragraph.

When all the beta cells in the pancreatic islets have been destroyed without hope of bringing them back to activity then a perfect control of the blood sugar does not benefit pancreatic function. This has been shown for alloxan diabetes (fibrotic degeneration of the islet cells) in experimental animals and by clinical studies. How to judge this state of affairs in patients is a difficult problem. The only available guide at the present moment is the knowledge that after total pancreatectomy in man the insulin requirement is not more than 30 to 40 units a day.<sup>9</sup> When this amount or more of insulin becomes necessary for the effective control of chronic diabetes then the clinician is justified in assuming that the pancreas has ceased producing insulin. Under such circumstances the middle of the road pattern of intermittent hyperglycemia appears warranted.

The insulin need of many diabetics above 40 units per day is attributed to a vague, unsatisfactorily explained condition termed insulin resistance. The specific means for the amelioration, let alone cure, for this disturbance, is not at hand. As a rule these cases do better with a restricted carbohydrate intake. When they take a high carbohydrate or a free diet their insulin requirement is prone to go up enormously. An elevated blood sugar without glycosuria may prevent restoration to normal of hydropic lesions in the beta islet cells. However, hyperglycemia in itself does not impair immunity, has little or nothing to do with the diabetic's state of resistance or susceptibility to infection, does not inhibit the growth of tissue culture, does not interfere with the healing of wounds or the recovery from infections, and promotes the metabolism of glucose.<sup>10</sup> Moreover, there is some evidence that a concentration of blood sugar greater than normal is necessary for the utilization of carbohydrates in diabetics.<sup>11</sup> Consequently, it would appear that hyperglycemia not associated with glycosuria, is objectionable only insofar as it has an unfavorable effect on the pancreas. This, in practice, would apply only to recent diabetics who have hydropic lesions, which are reversible, and to those chronic diabetics who have retained some insulin-producing islet cells—that is have an insulin requirement of less than 30 units. There is an apparent fallacy in this reasoning and that is the possibility of some remaining pancreatic tissue when the insulin requirement is 40 units or more because of concomitant insulin resistance. However it offers the best available starting point for the application of more relaxed types of treatment and relief from excessive nervous tension incident to the purist regime.

*Hypoglycemia.* Hypoglycemic, often called insulin, reactions result from a deficient supply of glucose to the brain. The viability of the tissues of the central nervous system depend upon the presence of glucose in the blood. When the blood sugar becomes very low—hypoglycemia—impairment of cerebral functions follows. Headaches, dizziness, sweating are among the first symptoms; progression to unconsciousness, convulsions and death may ensue. Besides the direct effect of hypoglycemia on the brain, the mal-effect and strain imposed by the outpouring of epinephrine engendered by blood sugar depression must be considered.

The lesions in the fatal cases are severe: petechiae and extensive cerebral hemorrhages, large areas of encephalomalacia and cyst formation.<sup>12</sup> It is self-evident that in diabetics who are subject to transitory hypoglycemic episodes, the morphological pathology cannot be determined. However, in experimental animals this can be done and months after recovery from hypoglycemic reactions, areas of demyelination, encephalomalacia and glial reactions are found.

All this leads to the conclusion that any hypoglycemic reaction, however mild, may entail petechial or larger hemorrhages that are prone to heal and leave no clinical effect, though some damage necessarily remains and may be cumulative with recurrent attacks. Not only the brain may be thus involved

but other tissues as well. I am thinking particularly about the eye grounds and the so-called diabetic retinopathy. Some cases of pheochromocytoma with paroxysmal hypertension have developed retinal hemorrhages. It is well established that hypoglycemic reactions are associated with a mobilization of epinephrine, thus being a potential cause of bleeding in the eye grounds.

This reasoning has been applied with apparent success to the treatment of diabetic retinopathy. Two cases may be mentioned. In each of them the hemorrhages were progressively aggravated and in each of them the bleeding ceased and the existing hemorrhages disappeared—in one patient with complete restoration of vision, and in the other with considerable improvement. The first was a young woman in her thirties. She had a “brittle” diabetes and could not be rendered sugar free without encountering hypoglycemic reactions; the insulin was so regulated from day to day that reactions were avoided, glycosuria was allowed but never to such a degree that polyuria occurred. The second was a man of 70; for one year he had recurring retinal hemorrhages; he had an attendant nurse and it was an easy matter to maintain a sugar-free urine and a normal blood sugar; he became subject to considerable dizziness which disappeared when a higher than normal blood sugar and a moderate glycosuria were established; simultaneously the retinal hemorrhages ceased and vision improved.

The avoidance of hypoglycemia furnishes a second means by which diabetic retinopathy and possibly other complications of diabetes may be prevented and rectified. The first was the maintenance of qualitative nutrition.

Every bit of evidence at hand points to the damaging effect hypoglycemic reactions probably have. Though there may be no signs of injury after many minor or even major low blood sugar incidents, it has to be conceded that their summation may lead to harm just as a prize-fighter who is struck on the head often enough becomes “punch drunk.” Furthermore, the fortuitous location of a hemorrhage has a distinct bearing. Bleeding may have little significance in a silent region of the brain, but in the motor areas may cause paralysis; in the periphery of the retinae, petechial bleeding goes unnoticed, whereas when the macular region is involved, loss of vision results.

For the above reasons when insulin is used the major consideration for the carrying out of successful long range treatment is the avoidance of hypoglycemic reactions. What has been stated concerning the vulnerability of the brain and the retinae to insulin over-effect, may also apply to the heart and the kidneys which are the other organs prone to be damaged in diabetes.

Recently it has been shown that all diabetics of 25 years' duration exhibit one or more complications: retinopathy, albuminuria, hypertension, myocardial degeneration.<sup>13</sup> Dolger has rendered a valuable service in collecting two hundred cases which yielded these results. Unfortunately from these observations the impression has been broadcast that all diabetics are afflicted

TABLE VI

## Blood Sugar—Regulation in Diabetes

A maintained normal blood sugar level will bring about a complete or partial reversal of the pancreatic lesions in diabetes of recent onset.

When diabetes becomes chronic and the insulin requirement exceeds 30 units, intermittent hyperglycemia and moderate glycosuria will usually not cause progressive damage to the pancreas.

Hypoglycemic (insulin) reactions are a cause for petechial and larger hemorrhages in the brain and retinae. The summation of repeated injuries of this sort may result in encephalopathy and retinopathy. The avoidance of hypoglycemic reactions therefore becomes of paramount importance. Such a step and the maintenance of qualitative nutrition are at present the only means suggested for preventing and remedying the complications of diabetes.

not only with complications but with complete physical disability. At the moment I can recall only three cases that have had diabetes for a quarter of a century. While all three have had complications which might be ascribed to diabetes, they are all active and in good health. One is a woman, aged 70, caring for her household and taking an extraordinary and effective interest in her children; one is a man, aged 68, employed in one of the large banks; and the third is a young woman who is the mother of four thriving children. There is no invalidism in any of these three diabetics. It is unduly pessimistic to regard all diabetics as doomed to inevitable decrepitude; a prospect for normal life and health is warranted for most of them.

## GLYCOSURIA

In diabetes glycosuria results from hyperglycemia. Consequently, as discussed under blood sugar, there are the diabetics of recent onset and the mild cases in whom a normal blood sugar and freedom from glycosuria may serve to heal hydropic lesions in the islet cells and prevent degeneration of pancreatic tissues from overstrain. Most clinicians agree on the desirability of a purist procedure in such patients. By some the same system of management is applied to all diabetics.

A moderate glycosuria, like hyperglycemia, is harmless when no functioning pancreatic tissue remains. The middle of the roaders recommend that there be no more than 10 to 20 grams of sugar in the urine per day and that the glycosuria be intermittent.<sup>14</sup> This is a sane, realistic recognition of the fact that diabetics are human beings and that the time and worry entailed in keeping the control of blood sugar and urine every hour of the day, every day of the year, is often not compatible with normal living. In some cases, especially elderly individuals, a constant glycosuria becomes a necessity because of hypoglycemic reactions at inordinately high blood sugar levels; in such instances the glycosuria should be maintained at a level of less than one per cent. Whenever glycosuria is sanctioned, special care must be exercised to check polyuria to the

These facts are not to be condoned limitless glycosuria while the diabetic receives protamine zinc insulin.<sup>15</sup> Tolstoi, the originator of this plan, believes that glycosuria may be

weight, freedom from all symptoms of diabetes: thirst, polyuria, frequency of urination, hunger, weakness, fatigue, polyphagia, pruritus of the genitals and visual disturbances; absence of ketone bodies in the urine. If these criteria are observed this actually ceases to be a new pattern for the treatment of diabetes, but means close adherence to the principles of the "middle of the roaders."

The fascinating simplicity and convenience of a free diet and limitless glycosuria have actuated doctors, patients and Tolstoi himself into carrying out a form of treatment that is contrary to valid principles of diabetes management. In practice the free dieters do not follow the rules set down in the original exposition of the "newer concepts in the treatment of diabetes mellitus." It is impossible to take up all the points in detail. Discussion will be confined to only one, that is polyuria. Polyuria existed in some of the cases published by Tolstoi.

Polyuria, loss of fluid and resulting desiccation have a far-reaching effect on the body economy. Outside of the well-known extreme dehydration and its devastating effect in diabetic coma there are comparatively few observations that bring home the results of desiccation. There are three striking ones which may be cited. It is well known that life without fluid is a matter of hours, while life without food lasts for days. In 1860 Weir Mitchell, one of the founders of functional neurology and the author of some excellent novels, showed that in frogs, hyperglycemia in itself had no effect upon the ocular lens, but when the excess of sugar was supplemented by desiccation, rapid formation of cataract took place which promptly disappeared when the frogs were immersed in water.<sup>16</sup> Ludwig Aschoff, one of the greatest pathologists, claimed that desiccation induces arteriosclerosis.<sup>17</sup>

An example of a patient arbitrarily taking on a free diet scheme is that of a girl, aged 14, who was under satisfactory control for her diabetes. While on a summer vacation for 10 weeks she relinquished all dietary precautions though maintaining her insulin injections. The daily insulin dosage was protamine zinc insulin 40 units and globin insulin with zinc 20 units by separate injections. The free dieting resulted in nocturia three times, indicating polyuria, a vaginal discharge, 2.5 per cent glucose in the urine, blood sugar 422 mg. per 100 c.c., and evident physical and mental deterioration. All these inroads were promptly rectified when a constant diet suitable to her needs and acceptable to her tastes was provided.

The interpretation of the free diet plan generally entertained by doctors is to allow all foods while insulin is administered. A tabulation, over a considerable period, of the effects of free diets as carried out under medical guidance, other than mine, yielded these data: Out of 56 females, nine developed pruritus vulvae, and out of 94 children, 11 became bed wetters when they had not been so before.

The teachings of Tolstoi have engendered the idea that the kind and amount of daily food may be adjusted to the patient's desire of the amount

and that limitless glycosuria is of no consequence while the diabetic receives protamine zinc insulin. Such a plan of treatment results in polyuria, pruritus vulvae and other symptoms of diabetes. If according to Tolstoi's original postulates, "freedom from all symptoms of diabetes," is to be achieved, the diet must be more or less constant and the glycosuria must be within reasonable bounds. In other words the free diet idea when applied in accordance with Tolstoi's "guiding principles" is, in reality, a middle of the road procedure and a warranted form of therapy for some but not all, diabetics. The free diet plan carried out according to lax and liberal interpretations is a menace to the diabetic patient.

TABLE VII

## Glycosuria—Regulation of Urinary Sugar in Diabetes

This largely parallels the statements made concerning hyperglycemia.

A maintained normal blood sugar level and freedom from glycosuria will bring about a complete or partial reversal of the pancreatic lesions in diabetes of recent onset.

When diabetes becomes chronic and the insulin requirement exceeds 30 units, then intermittent hyperglycemia and moderate glycosuria will not cause progressive damage to the pancreas.

In diabetics subject to hypoglycemic reactions at high blood sugar levels it is advisable to maintain a moderate glycosuria of less than 1 per cent.

The free diet plan, as usually interpreted and carried out, permitting limitless glycosuria, is a menace to the diabetic patient.

## SUMMARY AND CONCLUSIONS

A three-point plan for the management of diabetes is proposed. This embodies the advantages of all the current creeds for diabetes treatment and has a factual regard for the needs of the individual patient.

1. In diabetes of recent onset a normal blood sugar level and freedom from glycosuria are imperative for the rehabilitation of the injured cells in the pancreatic islets, also in those diabetics whose insulin requirement is less than 30 units, so that the remainder of the pancreatic tissue shall not be damaged by overstrain. A normal blood sugar concentration and avoidance of glycosuria are desirable in all cases but the paramount consideration is freedom from hypoglycemic reactions which may necessitate the countenancing of hyperglycemia and glycosuria, but never polyuria.

2. Conservation of qualitative nutrition as measured by the hemoglobin percentage, the red blood cell count and the level of the serum proteins; avoidance of quantitative over-nutrition, that is, obesity.

3. Adjustment of food intake, diet calculations, auto-urine analysis and medical supervision so that the diabetic will not be anxious, worried or hurried.

---

Free diets, as advocated and used at present, while the diabetic is receiving protamine zinc insulin, are prone to result in a harmful degree of glycosuria, polyuria and dehydration.

The publicized belief that all diabetics of long duration suffer from crippling complications is not substantiated in our experience. The avoid-

ance of polyuria (dehydration) and hypoglycemic reactions, and the maintenance of qualitative nutrition are the most effective means to combat the complications of diabetes.

## BIBLIOGRAPHY

1. JOSLIN, E. P., ROOT, H. F., WHITE, P., MARBLE, A., and BAILEY, C. C.: The treatment of diabetes mellitus, 1946, Lea & Febiger, Philadelphia, pp. 68-80.
2. BARKER, M. H., and KIRK, E. J.: Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, *Arch. Int. Med.*, 1930, xlv, 319-346.  
ALLEN, E. V., BARKER, N. W., and HINES, E. A., JR.: Peripheral vascular disease, 1946, W. B. Saunders Co., Philadelphia, p. 361.
3. MOSENTHAL, H. O., and MARK, M. F.: Advantages of protamine zinc insulin: Results in diabetes complicated by tuberculosis, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2652-2653.
4. WILDER, R. M.: Clinical investigations of insulins with prolonged activity, *Ann. Int. Med.*, 1937, xi, 13-30.  
TOLSTOI, E., and WEBER, F. C., JR.: Protamine zinc insulin: A metabolic study, *Arch. Int. Med.*, 1939, lxiv, 91-104.
5. LEWIS, L. A., SCHNEIDER, R. W., McCULLAGH, E. P., and CLARK, J.: Tiselius electrophoresis studies of plasma proteins in diabetes mellitus, *Jr. Clin. Endocrinol.*, 1944, iv, 535-539.  
SCHNEIDER, R. W., LEWIS, L. A., and McCULLAGH, E. P.: Plasma proteins. I. Alteration in diabetic retinitis, *Am. Jr. Med. Sci.*, 1946, ccxii, 462-465.
6. ALLEN, F. M.: Pathology of diabetes. IV. Role of hyperglycemia in production of hydropic degeneration of islands of Langerhans, *Jr. Metab. Res.*, 1922, i, 75-88.  
HAIST, R. E., CAMPBELL, J., and BEST, C. H.: The prevention of diabetes, *New England Jr. Med.*, 1940, ccxxiii, 607-615.  
LUKENS, F. D. W., and DOHAN, F. C.: Pituitary diabetes in the cat; recovery following insulin or dietary treatment, *Endocrinology*, 1942, xxx, 175-202.
7. BRUSH, J. M.: Initial stabilization of the diabetic child, *Am. Jr. Dis. Child.*, 1944, lxxvii, 429-444.
8. NEWBURGH, L. H., and CONN, J. W.: A new interpretation of hyperglycemia in obese middle-aged persons, *Jr. Am. Med. Assoc.*, 1939, cxii, 7-11.  
NEWBURGH, L. H.: Control of the hyperglycemia of obese "diabetics" by weight reduction, *Ann. Int. Med.*, 1942, xvii, 935-942.
9. RICKETTS, H. T., BRUNSCHWIG, A., and KNOWLTON, K.: Effects of total pancreatectomy in a patient with diabetes, *Am. Jr. Med.*, 1946, i, 229-245.
10. MOSENTHAL, H. O.: Hyperglycemia: Evaluation in treatment of diabetes mellitus, *Jr. Am. Med. Assoc.*, 1935, cv, 484.  
BAYNE-JONES, STANHOPE: The effects of carbohydrates on bacterial growth and development of infection, *Bull. New York Acad. Med.*, 1936, xii, 278.  
HIMWICH, H. E.: Blood sugar in experimental diabetes, *ibid.*, 1936, xii, 284.  
TOLSTOI, EDWARD: Blood sugar in diabetes mellitus, *ibid.*, 1936, xii, 295.  
RICHARDSON, R.: Immunity in diabetes. III. Relation of tissue glycogen and blood chemistry to bacterial dissemination, antibody formation and survival after infection in diabetes, *Jr. Clin. Invest.*, 1940, xix, 239-250.
11. SOSKIN, S., and LEVINE, R.: Carbohydrate metabolism, 1946, University of Chicago Press, Chicago, p. 185 and p. 253.
12. BAKER, A. B.: Cerebral lesions in hypoglycemia. II. Some possibilities of irrevocable damage from insulin shock, *Arch. Path.*, 1938, xxvi, 765-776. III. Experimental investigations, *Arch. Path.*, 1939, xxviii, 298-305.  
SAKS, A. L., and ALEXANDER, L.: Fatal hypoglycemia: Clinicopathologic study, *Arch. Neurol. and Psychiat.*, 1939, xlii, 286-297.



13. DOLGER, H.: Clinical evaluation of vascular damage in diabetes mellitus, *Jr. Am. Med. Assoc.*, 1947, cxxxiv, 1289-1291.
14. JOHN, H. J.: The treatment of diabetes: Use of protamine and crystalline insulin, *New York State Jr. Med.*, 1938, xxxviii, 1266.  
HANDELSMAN, M. B.: Variations in the response of diabetics to insulin therapy, *New York State Jr. Med.*, 1943, xliii, 2287-2293.  
JOSLIN, E. P., ROOT, H. F., WHITE, P., MARBLE, A., and BAILEY, C. C.: The treatment of diabetes mellitus, 1946, Lea & Febiger, Philadelphia, p. 348.  
ANDERSON, G. E.: A creed for the treatment of diabetes, *Am. Jr. Digest. Dis.*, 1947, xiv, 170-178.
15. TOLSTOI, E., and WEBER, F. C., JR.: Protamine zinc insulin: A metabolic study, *Arch. Int. Med.*, 1939, lxiv, 91. Protamine zinc insulin: A clinical study, *Arch. Int. Med.*, 1940, lxvi, 670.  
TOLSTOI, E., ALMY, T. P., and TOSCANI, V.: Treatment of diabetes mellitus with protamine insulin: Is a persistent glycosuria harmful? A metabolic study of a severe case, *Ann. Int. Med.*, 1942, xvi, 893.
16. MITCHELL, S. W.: On the production of cataract in frogs by the administration of sugar, *Am. Jr. Med. Sci.*, 1860, xxxix, 106-110.
17. ASCHOFF, LUDWIG, in COWDRY, E. V.: Arteriosclerosis, 1933, Macmillan Company, New York.

# THE PROGNOSTIC SIGNIFICANCE OF THE "GUILLAIN-BARRÉ SYNDROME" \*

By MORTON HAND, M.D., and MARTIN RUDOLY, M.D., *Brooklyn, New York*

TWENTY years after the original description<sup>1</sup> of a clinical entity familiarly known as the Guillain-Barré syndrome, Guillain proposed to "delimit as exactly as possible"<sup>2</sup> the syndrome isolated in 1916, so that it might be "kept distinct from (the remainder of) the broad group of polyradicular neuritides with nonfatal outcome" which are seen quite often in neurological practice. In 1937, however, Guillain revoked his opinion of a year before without reservation. Nevertheless, it seems advisable to reaffirm Guillain's original position because wartime experience with a distinctive group of cases appears to bear out his original contention that the disease can be "delimited." Furthermore, it appears necessary so to delimit this syndrome in order to avoid confusing it with related conditions.

The advantages of such clinical isolation are facilitation of the study of etiological factors, of the course of the disease, of its response to treatment, of the incidence of serious complications and of the prognosis. Although nosologic considerations are not the aim of such delimitation, their importance in the analysis of factors which will yield additional knowledge of the disease is recognized.

This presentation will describe the occurrence of remissions and exacerbations in this disease, such remissions and exacerbations having been considered unusual in inflammatory disease of the nervous system. Etiologic relationships with throat infections such as tonsillitis, exudative pharyngitis of streptococcic or diphtheritic origin, and pyemia will be apparent. Evidence is presented which suggests that the sulfonamides used in treatment of these primary infectious conditions may on occasion constitute the etiological agent in the neurologic syndrome.

That involvement of the "final common pathway" often accounts for "bulbar" and "bladder" disturbances which in this series were not indisputably due to implication of the central nervous system is obvious. The central nervous system may be involved, but clinically such implication is masked by disturbance of peripheral nerves, so that involvement from cerebral cortex to spinal cord pathways may be predicated but not proved.

The occurrence of albumino-cytologic dissociation in this syndrome and not in other inflammatory diseases of the nervous system has not been explained.<sup>3, 4, 5, 6</sup> This laboratory finding is the prominent differentiating feature of the disease. Conditions in which disturbance of the nervous system are due to toxins show little or no alteration in total protein content of the cerebrospinal fluid.

\* Received for publication June 2, 1947.

From the Neuropsychiatric Service of the 37th General Hospital.

Most of the cases occurring among American troops were not seen at the onset of their illness. They came under observation several weeks after the onset of the "paralytic" stage and several were followed to complete recovery, including two patients who were returned to duty. None of the patients died or were left with disabling residua.

Cases occurring in German troops gave evidence of progressive improvement. None was seen at the onset of illness and the laboratory data obtained earlier in their illness were obtained from German hospital records. The findings were discussed with German Medical Officers who regarded them as accurate and reliable.

Two cases seen on the neurological service of Kings County Hospital, Brooklyn, New York, are briefly described in order to compare them with cases seen abroad in military service and to note their similarity.

#### CASE REPORTS

*Case 1.* The first case illustrates the typical symptom complex with remissions and exacerbations.

A 23 year old soldier stated that he had suffered an attack of tonsillitis on October 5, 1943. Throat smears on October 9 and October 16 revealed no diphtheria bacilli.

On October 22, 1943 the patient experienced swallowing difficulty which progressed so that, on admission to the hospital, he was unable to swallow without gagging or returning fluid through his nose. The voice had a nasal twang, the palate was weak, and there was evidence of recent weight loss. The spinal fluid protein was 64.8 mg. per cent; and no cells were observed. Examination was otherwise negative. The patient was tube-fed for two weeks and recovered "bulbar" control. On December 1, 1943 he complained of general weakness and visual disturbance and again of difficulty in swallowing. The tendon, abdominal and cremasteric reflexes were not obtained. Moderate weakness of all extremities and slight flattening of the right side of the face were noted. There were no sensory alterations. On December 4 these signs were noted together with loss of muscle, joint, tendon and vibratory sensibility in the lower extremities. The spinal fluid protein was 98 mg. per cent. The intensity of weakness increased, and by December 13, 1943 the patient again had to be tube-fed. There was diffuse and severe atrophy of all muscles of the extremities, and of the temporal, rectus capitis, sternomastoid, trapezius and paravertebral muscles on both sides. The tongue was atrophied, and there was bilateral facial weakness. The patient was unable to hold his head erect, sit, move his jaws, chew, swallow, speak above a whisper, or move his extremities. It was necessary to suction mucus from the pharynx and change his position repeatedly for more than a week. He then began to regain his strength.

By December 21 he was able to speak with moderate vocal resonance. Position and vibratory sensibility remained impaired. Painful and thermal stimuli were not perceived distally in all four extremities. By December 28, there was additional improvement in muscular strength in the extremities but a loss of all modalities of sensation in the upper extremities was now noted. There was return of power of the pharyngeal muscles but tube feeding was still necessary. Weakness of the extraocular muscles kept the eyeballs immobile.

By January 15, 1944 swallowing difficulty had ceased and motor power improved in the arms, so that the patient could lift his arms and flex his elbows. Wrist and foot drop were bilaterally present. The voice was normal. There was considerable

return of sensibility in the extremities, but the patient complained of burning sensations in his legs. The atrophy and areflexia persisted. Spinal fluid protein was 117.9 mg. per cent. During February and March 1944, there occurred progressive improvement in motor power and muscle volume. All modalities of sensation improved but vibratory sensibility continued to be somewhat impaired. At the time of transfer to a hospital in the United States, the patient was able to stand and walk and the tendon jerks were present, but weak and exhaustible. He continued to complain of burning sensations in the hands and feet. Laboratory studies at this time revealed a normal electrocardiogram, blood and spinal fluid. The spinal Wassermann reaction was negative.

*Case 2.* This case showed progressive muscular involvement with exacerbations.

The patient, a 22 year old soldier, stated that he "had a cold" on November 27, 1943, and two days later experienced numbness in his toes and legs which spread to his body, then to his finger tips and arms. The tongue began to feel numb, he lost the sense of taste, had difficulty in swallowing, and regurgitated fluid through the nose. On December 3, 1943 he experienced blurring of vision and diplopia. He stated that he could walk well until January 10, 1944. When examined on January 18 he was bedridden, emaciated, and required tube feeding. He spoke hoarsely with a nasal twang and exhibited slight bilateral facial weakness. The muscles of the pharynx were paralyzed and its mucosa was insensitive. The patient could neither hold his head erect nor turn it from side to side. The tongue appeared normal. Motor power of all four extremities was weak, the muscles appearing shrunken and atrophied. Tendon jerks in the upper and lower extremities, and cremasteric and abdominal reflexes could not be elicited. A left Babinski response was produced. Pin prick and cotton touch perception were diminished throughout the body, especially in the perioral, perianal, genital areas and in the distal portions of the extremities. Vibration was not perceived over the extremities. All laboratory studies were negative except for the finding of 76.4 mg. per cent of total protein in the cerebrospinal fluid.

Because of pharyngeal weakness, the patient had difficulty in expectoration and aspirated mucus. On January 22, 1944 atelectasis of the right lung was noted when the patient suddenly became comatose, cyanotic and dyspneic. Bronchoscopic aspiration followed by stimulant drugs, oxygen by nasal catheter, and postural drainage were required as immediate lifesaving measures. From that date there was progressive improvement. Muscle power returned slowly and all modalities of sensibility progressively improved. At the end of March, 1944 the patient was free of swallowing difficulties and could walk quite well. However, although the abdominal and cremasteric reflexes were elicited, no tendon reflexes could be obtained, and the Babinski sign on the left persisted.

*Case 3.* The patient was a 34 year old soldier who developed a sore throat on November 7, 1943 and was ill for two weeks. During this period there was an exudate on the soft palate and on the left tonsil. Smears examined for the diphtheria bacillus were negative. Sulfadiazine was administered from November 11, 1943 to November 27, 1943, but was discontinued when the patient began to complain of precordial pain. On December 7, 1943 he developed numbness of the face, lips, fingers and toes. He "lost" his voice, had difficulty in swallowing, regurgitated fluid through the nose, and suffered "blurring of vision." At this time examination disclosed diminished motor power in all extremities, diminished tendon jerks at the elbows, ankles and knees, and diminished sensitivity to touch and pin prick on the tongue and in all four extremities. On January 13, 1944 there was loss of vibratory and position sensibility of all extremities, marked weakness of the muscles of the extremities and trunk, and loss of weight. There was also imperception of urination, facial weakness on the right, loss of touch and taste sensation of the tongue and buccal mucosa. A right Babinski sign was present.

Laboratory examinations showed normal findings except for the cerebrospinal fluid which had a total protein content of 74.7 mg. per cent with no cells.

Weakness persisted during the next six weeks except for a slight return of power in the lower extremities. The deep tendon reflexes were not elicited, and atrophy of the extremities with loss of sensation was noted at the time of transfer.

*Case 4.* The patient was a young infantry soldier who had a sore throat early in November of 1943. On November 16, 1943 he noted stiffness, weakness and sharp pains in the legs, and difficulty in walking. He was given routine tetanus toxoid and a typhoid vaccine injection on this date along with the other members of his unit. His complaints continued and on November 20, 1943 he was hospitalized. Examination disclosed blurred optic disc margins bilaterally, unobtainable tendon reflexes at the elbows, ankles and knees, flaccid paralysis of the lower extremities, marked weakness of the upper extremities more severe distally, atrophy of the musculature of the extremities, and diminution to absence of all modalities of sensibility in the extremities, more severe distally.

An increase in motor power occurred during hospitalization so that by January 21, 1944 the patient could sit up, move his legs, and use his arms. There was some return of pain and temperature sensibility but vibratory and joint position sensibility continued diminished.

Laboratory findings. Cerebrospinal fluid total protein: November 30, 1943—310 mg. per cent, December 8, 1943—338 mg. per cent, January 13, 1944—156.8 mg. per cent. Electrocardiograph, December 1943, indicated slight myocardial damage on the basis of "abnormal" T-waves and sinus tachycardia. There was gradual restoration of power and sensation so that the patient was walking normally at the time of transfer and had only slightly diminished sensation in all modalities.

*Case 5.* The patient was a 24 year old soldier who had an attack of tonsillitis with a white patchy pharyngeal exudate in October of 1943. One month later he noticed numbness and shooting pains in the legs which increased until November 20, 1943, when he had difficulty in balance while walking. He began to regurgitate fluid through his nose when swallowing. When he was hospitalized on January 3, 1944 he complained of numbness of fingers and feet, and said that his legs "felt like wood." He had lost 20 pounds in two months and slapped his feet when he walked. Examination revealed blurring of the optic discs bilaterally, diminution of all modalities of sensation in the distal portions of the extremities, atrophy of the muscles of the trunk and extremities, unobtainable tendon reflexes at the elbow, knee and ankle joints, and no abdominal or cremasteric reflexes.

Laboratory studies revealed cerebrospinal fluid total protein of 66.1 mg. per cent on January 13. There was gradual improvement in muscle tone and strength so that by April 1944, the patient walked fairly well. The tendon reflexes were present but weak at that time. There still remained evidence of impairment of joint position and vibratory sensibility in the legs.

The following case illustrates an exacerbation of symptoms after partial recovery.

*Case 6.* The patient was a 25 year old soldier who had "Sandfly fever" on August 14, 1944. He complained of headaches, general malaise and fever. On August 17 he was hospitalized because of weakness and numbness of the extremities, paralysis of the facial muscles, and difficulty in swallowing. During the next five days he improved. He was able to walk and had no difficulty in swallowing. On August 22 he suddenly collapsed while walking and gradually became weaker. He complained of blurring of vision and inability to feel his legs. On August 27 a pink macular rash appeared on his chest, abdomen and arms. He was unable to move his eyes and he had a bilateral lid ptosis with facial diplegia and a weak, trembly voice. Examination

revealed loss of all modalities of sensation in all four extremities distally to the elbows and knees, and unobtainable tendon jerks at the elbows, knees and ankles.

There was gradual but asymmetrical improvement from this time until November 28, 1944, when he was transferred. At this time he presented weakness of both lower extremities, and loss of pain sensibility on the left side of the face and on both feet and hands, paresis of the left side of the face, absent tendon jerks at the elbows, knees and ankles. The cerebrospinal fluid on August 14 revealed a total protein of 70 mg. per cent; 246 mg. per cent August 28, 1944, 114.6 mg. per cent September 10, 1944, 149.25 mg. per cent October 25, 1944, 160 mg. per cent November 20, 1944.

*Case 7.* The patient was a 30 year old Sergeant who suffered from boils in both axillae in November 1944. He received 60 injections of penicillin in December 1944 and during this period he suffered from a severe sore throat. On January 10, 1945 he noted weakness of his extremities, awkwardness in gait, clumsiness of his hands and fingers, and blurring of vision. His speech became thick and hoarse, his lips and tongue became insensitive. He was admitted to the hospital on February 17, 1945. Examination revealed weakness and loss of fine movements in the extremities, absent tendon jerks at the elbows, knees, and ankles. The left cremasteric and abdominal reflexes were not elicited. Pin prick was poorly perceived distally in all four extremities, more so on the left. Laboratory examination revealed only an elevated total protein in the cerebrospinal fluid of 78 mg. per cent on February 17, 1945.

*Case 8.* A 41 year old soldier entered the hospital for dermatitis January 4, 1945, and on January 17, 1945 developed a non-diphtheritic exudative tonsillitis which soon subsided. On February 16, 1945 he noticed that his left eye "watered" and several days afterward the left side of his face became "weak." He then developed progressive numbness of the hands and feet and arms and legs. His penis felt numb and the urinary stream "lost force." He became constipated and had "sore muscles." He began to suffer difficulty in swallowing and speaking clearly and he staggered while walking, losing his balance when arising from sitting positions. His hands became clumsy. Examination revealed weakness in all extremities, absent tendon jerks at the knees and ankles, diminished sensibility to pin prick, touch, vibration and change of position in all four extremities, more marked distally. The spinal fluid total protein was 51 mg. per cent on February 26, 1945, and 76.8 mg. per cent on March 7, 1945. Improvement was gradual until the time of transfer on April 25, 1945. At that time he was able to walk and had fair use of his hands and fingers with return of sensibility in the hands and feet.

*Case 9.* A 32 year old soldier with a chronic anxiety state complained of weakness, stiffness and numbness of the extremities which began one month after the onset of a "diphtheritic" sore throat in May of 1944. At this time he had difficulty in swallowing. His "food stuck in his throat and he talked through his nose." When he was hospitalized for these complaints on June 6, 1944, he presented a nasal twang, weakness, areflexia and diminished sensibility in all extremities. All throat smears were negative for diphtheria. From June 10 to July 4, 1944 his weakness increased so that he became bedridden. Thereafter improvement in power and sensibility was progressive until the middle of August when the reflexes began to return and sensibility increased. He was discharged to duty September 10, 1944 with normal reflexes and no sensory disturbances. Six weeks later he was returned to the hospital because of his chronic anxiety state. At this time the reflexes were 2-plus, there were no complaints of weakness or numbness of the extremities, and no sensory impairment was noted. Spinal fluid studies revealed total protein of 136 mg. per cent on June 12, 78.5 mg. per cent on July 14, 1944.

*Case 10.* A 29 year old Lieutenant entered the hospital on June 28, 1944 for tonsillitis from which he recovered. On July 11, 1944 tonsillectomy was performed. He was seen on the neurological service for the first time on July 16, 1944 because he had reported numbness of the hands. At this time he stated that on May 4, 1944

he had had a sore throat and saw white patches in the pharynx upon looking into the mirror. He had had similar sore throats one year previously in Sicily and on frequent occasions since the age of eight before entering military service.

On May 4 he noted weak and numb feelings in all extremities. On June 7 he regurgitated fluids through the nose and his throat felt numb. He found that he was unable to taste food and his speech was indistinct. On June 20 he stumbled and staggered but the numbness of the throat had subsided and his speech had improved. He no longer regurgitated and numbness was not felt in the upper extremities, although it persisted in the lowers.

Examination revealed that the patient waddled and stumbled while walking. He used his hands awkwardly in fastening and unfastening his clothing. The speech was muffled. The gag reflex was present. The tendon reflexes were not obtained. The abdominal and cremasteric reflexes were present but weak and exhaustible. Power was diminished about 25 per cent at all joints. Light touch, pain and thermal sensibility were easily perceived throughout the skin areas. Bathydysesthesia was present in the feet and hands. The spinal fluid was clear, contained 2 cells per cu. mm., 75.5 mg. per cent glucose, and 73.1 mg. per cent total protein.

Two weeks later the patient stated that he felt better but had fallen on several occasions when he went to the latrine or mess hall. His "voice tired quickly" and paresthesia was no longer experienced in the pharynx or extremities. The clinical signs were unaltered. Over a period of two weeks power rapidly diminished in all extremities so that he was unable to feed himself or alter the position of the extremities or trunk in bed. The clinical signs were unaltered except for greater loss of power. The spinal protein was 49.7 mg. per cent on August 18. By the end of August power had begun to return in all extremities. On the last of September when he returned to duty at his own request, the only complaint was "tiring of the hips after walking a couple of miles." The reflexes were not obtained at this time and all modalities of sensibility were slightly diminished in the distal portions of the extremities.

The patient returned for examination on November 10, 1944, after "hiking all over Italy." He stated that he still "felt it in the hips" after climbing hills. The reflexes were 2-plus throughout, and sensibility was slightly impaired in the toes. Motor power appeared normal at all joints and no atrophy was noted in the hip muscles.

*Case 11.* A 20 year old soldier developed weakness and paresthesia of the extremities, retention of urine, constipation, muscular pains, and mild difficulty in swallowing in October 1944. The deep reflexes were not obtained and all modalities of sensibility were diminished in all extremities. Total protein in the spinal fluid varied from 85 to 160 mg. per cent during the six weeks he was observed. There was some return of power and sensibility at the time of evacuation from Italy but he was bedridden when transferred.

In the following five cases the appearance of the neurological symptoms followed clinical diphtheria.

*Case 12.* The onset of swallowing difficulties, weakness of the extremities and paresthesias occurred one month after pharyngeal diphtheria. There was diminished power and areflexia in all four extremities, diminished sensibility in all modalities in the distal portions of the extremities, perioral and perianal regions. Spinal fluid protein was 45.3 mg. per cent and 58.8 mg. per cent. Sensibility returned and power was gradually increasing at the time of transfer, three months later.

*Case 13.* Three months after an attack of pharyngeal diphtheria this patient suffered accommodation difficulty and weakness of the extremities. There was diminished sensibility of the hands and feet and unobtainable tendon reflexes. Spinal

fluid total protein was 68.2 mg. per cent. Gradual improvement in power and sensibility occurred during two months' observation until the time of transfer.

*Case 14.* Pharyngeal diphtheria in December 1944 was followed in three weeks by difficulty in enunciation and swallowing. Five weeks later paresthesias and weakness in all extremities occurred. There was diminished vibratory sensibility in the hands and feet and areflexia on examination five months after onset. Power was diminished but improving. Spinal fluid total protein was 28.2 mg. per cent.

*Case 15.* The patient suffered a diphtheritic sore throat and two weeks later noted difficulty in visual accommodation. There was progressive involvement of the extremities by diminished sensibility in all modalities and diminution of tendon jerks. Spinal fluid total protein was 44.5 mg. per cent. Gradual return of sensibility and power occurred in four months.

*Case 16.* The patient had a pharyngeal diphtheritic infection on January 2, 1945. On January 22, 1945 he noted difficulty in accommodation. On February 8, 1945 he presented complaints referable to swallowing and speech and weakness of the arms and legs. Examination revealed areflexia at the elbows, knees and ankles and diminished sensibility in all modalities in all four extremities. Spinal fluid total protein was 38.6 mg. per cent in March, 1945 and 37.4 mg. per cent in June, 1945. Progressive improvement in power and sensibility occurred during three months to the time of transfer.

The following four cases occurred in association with large (self prescribed) dosage of sulfonamides.

*Case 17.* This patient developed weakness and paresthesias of the extremities two weeks after unlimited use of sulfonamide drugs. There occurred areflexia, and diminution of all modalities of sensation in the extremities, confinement to bed for three months, and gradual recovery in six months. Spinal fluid total protein was 32 mg. per cent during the period of greatest disability.

*Case 18.* Two months after unlimited dosage with sulfonamide drugs the patient developed weakness, areflexia, paresthesias and diminished sensibility in the extremities. Gradual recovery was noted in five months. Total protein in the spinal fluid was 29.6 mg. per cent during the period of greatest disability.

*Case 19.* Six weeks after unlimited dosage with sulfonamide drugs the patient developed weakness, areflexia and diminished sensibility in all extremities. Total protein in spinal fluid was 23.0 mg. per cent in May of 1945 and 45.0 mg. per cent in June, during the period of greatest disability. Gradual improvement occurred during July and August.

*Case 20.* Two weeks after unlimited ingestion of sulfonamides this patient developed areflexia, marked weakness, diminished sensibility in all modalities in all extremities. Total protein in the spinal fluid was 32 mg. per cent during the period of greatest disability. Gradual recovery was observed during a three month period.

*Case 21.* This patient developed weakness and clumsiness of the extremities one month after a severe sore throat. He suffered diminution of sensibility in all modalities in the extremities and there was areflexia at the elbows, knees, and ankles. Spinal fluid total protein was 160 mg. per cent. Gradual improvement occurred over a period of two months so that he was able to walk when discharged, though he still presented areflexia and sensory disturbances in the hands and feet.

*Case 22.* This 19 year old girl developed pyoderma on February 15, 1946 and was treated with penicillin. On February 25, 1946 she noted difficulty in accommodation. On April 11, 1946 she suffered weakness of all extremities and numbness and diminished sensibility in all modalities in all four extremities. There was imperception of urination. On May 9, 1946 she had difficulty in speech and swallowing and increased weakness of her limbs so that she became bedridden. From that point she



improved progressively to complete recovery in July 1946. Spinal fluid protein was 125 mg. per cent April 13, 1946; 126 mg. per cent May 1; 173 mg. per cent May 18; 101 mg. per cent on June 8, 1946; and 40 mg. per cent on July 10, 1946.

### COMMENT

Among the 11 cases of American soldiers with polyneuritis there were 10 who had a definite history of pharyngitis, six with an exudate, which preceded the onset of neurological disturbance by three to six weeks. All were characterized by diminution of motor power, reflexes and sensibility in the extremities. Accommodation and swallowing difficulties were common at the onset and some urinary disturbances were noted. Elevation of the total protein content of the spinal fluid without increase of cells was present in every case. Five cases of polyneuritis were seen among German prisoners of war whose throat smears revealed the presence of the diphtheria bacillus. In these patients the total protein of the spinal fluid was normal or only very slightly elevated. Similarly, in the four German prisoners with polyneuritis associated with extraordinary ingestion of sulfonamides over a long period there was no elevation of the total protein level in the spinal fluid.

Fever was not present in any of the cases in association with the neurological disability but was present in rare instances at the time of throat infection weeks before. Spontaneous pains or burning sensations occurred but were not common in this series.

In general the total protein level in the spinal fluid was high at the height of the symptomatology and decreased as the signs and symptoms of polyneuritis subsided. The first evidence of progressive recovery usually occurred two or three months after the onset. Few of the patients appeared acutely ill, but severe motor disability confined many to bed in a helpless state, and complications resulting from palatal paralysis and swallowing difficulty threatened life in two instances.

Treatment consisted of bed rest, physiotherapy from the onset of motor weakness, thiamine chloride 300 mg. daily with a high vitamin diet. Activity was permitted to the extent of the patient's capability. This was an adjunct to the physiotherapy and had as its aim the prevention of muscular deterioration.

The pattern of the disease may be described as follows: Following recovery from a suppurative sore throat, exudative skin lesion, purulent skin or lymph node infection there occurs a rather sudden onset of weakness and numbness of the extremities after a latent period of several days or weeks. With the disability in the limbs there is often disturbance in visual accommodation and in swallowing. The facial muscles may become paralyzed, and then there may occur progressively increasing involvement of sensibility and motor power, first in the extremities then in the trunk. Occasionally, because of imperception of urination there may be dribbling or retention. Some improvement may occur, following which a sudden relapse may render

the patient helplessly bedridden. The course is afebrile throughout and the prognosis for complete recovery excellent.

Gordon Holmes<sup>7</sup> in 1917 described a group of cases among soldiers which gave no evidence of cerebrospinal fluid changes. He called the disease acute febrile polyneuritis. In 1918, Brandford, Bashford and Wilson<sup>8</sup> described cases under the same classification and in their series the spinal fluid was also normal. In 1919 Casamajor<sup>9</sup> and Kennedy<sup>10</sup> described a similar disease picture. The syndrome encountered in this series among American patients both abroad and in the United States was described recently in illustrative case presentation by Mackay,<sup>11</sup> by pathologicoanatomic studies intended to determine the etiological agent by Lassen, Ipsen and Bang,<sup>12</sup> by Lewey,<sup>13</sup> and by Lowenberg and Foster.<sup>14</sup> As mentioned above, the original description by Guillain, Barré and Strohl<sup>1</sup> corresponded with the conditions observed in this series.

The comprehensive review by DeJong<sup>15</sup> probably includes related though separate syndromes from that seen in this group of patients, since it described cases in which the entire nervous system was generally involved. Among our patients no definite clinical evidence of other than peripheral nerve and nerve root involvement was obtained. Cases in which peripheral nerves from the brain stem were involved in several of our patients represented the most serious of the entire series.

The cases occurring among American soldiers and civilians were considered to be caused by a toxic or infectious agent. Since practically every case was preceded by some throat infection (table 1) followed by a variable but limited latent period (table 2), the infection was predicated as instrumental in the cause of the neuropathy. Vitamin deficiency was eliminated as a possible causal factor since all patients had a history of a diet superabundant in vitamins, and although vitamins were administered, no definite improvement could be ascribed to such therapy.

In its third report, the Matheson Commission<sup>16</sup> suggested that the Guillain-Barré syndrome may be a virus disease allied to epidemic encephalitis

TABLE I  
Preceding Infections

	German	American
1. Cold or sore throat before onset	1	4
2. Membrane or exudate in throat before onset	3	5
3. Skin or lymph node infection before onset	1	1
4. Other	3 (Gonorrhea)	1 Sandfly fever

TABLE II  
Incubation Period after "Predisposing" Infection or Medication

	German	American
1-7 days	1	2
7-21 days	6	5
21 days or more	1	5
Unknown	1	1

TABLE III  
Chief Symptoms and Signs

	German	American
Swallowing difficulty	2	8
Visual accommodation difficulty	4	5
Weakness and numbness of extremities	6	8
Sphincteric disturbances	0	2
Babinski positive	0	2
Myocardial involvement	1	1
Facial palsy	0	4
Pains sharp or shooting	0	3
Muscle tenderness	0	1
Muscle atrophy	1	4
Palatal paralysis	3	5
Absent deep reflexes	7	12
Diminished sensibility in the extremities	5	12

lethargica. Barker, Cross and Irwin,<sup>17</sup> and Beriel and Devic<sup>18</sup> believed that polyradiculoneuritis ought not to be considered a peripheral form of epidemic encephalitis. Guillain's<sup>2</sup> conception was similar. Barré<sup>19</sup> suggested an as yet unknown organism or virus.

No pathological material was obtained in our cases since all recovered. Guillain and Barré's cases also recovered. DeJong's review<sup>15</sup> reported the pathological findings of several investigators. No consistency in the findings was noted, however. Hecht<sup>20</sup> and Taylor and McDonald<sup>21</sup> described lesions in the gray matter of the spinal cord and cerebral hemispheres and the latter report described the changes as inflammatory in nature. Gilpin, Moersch and Kernohan<sup>22</sup> saw no evidence of inflammation. The changes they observed were degenerative and most marked in the peripheral nerves with slight spinal cord involvement, particularly in the anterior horns of the gray matter. The predominant alteration was edema with myelin degeneration and fragmentation of the axis cylinders in the peripheral nerves. Barker,<sup>23</sup> Alajuanine,<sup>24</sup> Garvey and Slavin,<sup>5</sup> and others suggested that the pathology might be due to inflammation of the sheath of Schwann where there occurs an increase in the number and volume of the sheath cells with diffuse lymphocytic infiltration of the nerve roots, peripheral nerves and of the myelin sheath. They believed that the responsible agent was a filtrable virus. There is, therefore, no general agreement as to the underlying pathological changes. Most workers described degenerative changes involving the nerve roots and peripheral nerves and secondary degenerative alteration in the anterior horn cells. No definite evidence of inflammatory reaction has been shown either in the nerve, nerve root, meninges, gray matter of the spinal cord, or in myelin sheaths. Furthermore, there is no evidence of glial proliferation or infiltration within the spinal cord.

In considering the differential diagnosis, the sudden occurrence of flaccid paralysis sometimes occurring with muscle tenderness and meningeal irritation may suggest anterior poliomyelitis. The minimal febrile reaction, symmetry of limb involvement, and the occurrence of subjective and objective sensory change differentiate the syndrome clinically. The spinal fluid

findings offer definite diagnostic evidence. Heavy metal poisoning and neuritis with avitaminosis can be ruled out by the clinical course, spinal fluid findings, absence of response to vitamin therapy or of history of exposure to the metals.

As has been shown in this presentation, however, post-diphtheritic neuritis closely resembles the Guillain-Barré syndrome. Differentiation depends on demonstration of the diphtheria bacilli and on the relatively slight elevation of spinal fluid total protein.

Since the etiology is unknown, treatment has been palliative and empirical, and no specific measures are applicable. The use of thiamine chloride, early application of physiotherapy, and fever therapy in order to reduce the period of disability and shorten convalescence have been suggested by Straus and Rabiner.<sup>25</sup> Most important is the prevention of complications due to swallowing difficulty and bladder dysfunction, such as aspiration pneumonia, asphyxia, atelectasis, or ascending urinary infection. Since the disease seems to be self limited, the patients improve despite lack of specific treatment. However, death was narrowly avoided in two cases of this series. It may be possible to avoid fatalities by zealously watching all cases with swallowing or respiratory difficulty and providing apparatus for tube feeding, artificial respiration and bronchoscopy for possible emergencies in these patients. The fatal cases described by DeJong<sup>15</sup> were due to "bulbar" and "diaphragmatic" failure. Those presented here had "bulbar nerve" paresis both motor and sensory. They required suction and tube feeding. They complained of facial and perioral anesthesia and paresthesia. Perhaps because the lesions were not within the brain stem these cases could be successfully tided over the paralytic phase by unremitting nursing care. In true bulbar involvement which probably did not occur in the syndrome described in this presentation, such measures usually fail. DeJong<sup>15</sup> reported changes in the motor nuclei in the medulla and anterior horn cells in two cases with fatal outcome. Gilpin, Moersch and Kernohan<sup>22</sup> found no abnormalities in the anterior horn cells, brain stem, cerebellum, basal ganglia or cerebral hemispheres, but did find degenerative changes in the peripheral nerves including the peripheral portions of the cranial nerves. The cases in both reports were clinically comparable. It is likely that many cases with symptoms of "bulbar" involvement are explainable on the basis of disease in the peripheral nerves emanating from nuclei in the brain stem.

#### BIBLIOGRAPHY

1. GUILLAIN, GEORGES, BARRÉ, J. A., and STROHL, A.: Sur un syndrome de radiculo-né vrité avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire; remarque sur le caractères cliniques et graphiques des reflexes tendineux, Bull. et mém. Soc. méd. de hôp. de Paris, 1916, xl, 1462.
2. GUILLAIN, GEORGES: Radicular neuritis with acellular hyperalbuminosis of the cerebrospinal fluid, Arch. Neurol. and Psychiat., 1936, xxxvi, 975.
3. MERRITT, H. H., and FREMONT-SMITH, F.: The cerebrospinal fluid, 1937, W. B. Saunders Company, Philadelphia, pages 180-185.

4. PINCKNEY, C.: Acute infective polyneuritis, *Brit. Med. Jr.*, 1936, ii, 333.
5. GARVEY, P. H., and SLAVIN, H. B.: Acute infectious polyneuritis, *Internat. Clin.*, 1938, iv, 38.
6. COLLIER, J.: Peripheral neuritis, *Edinburgh Med. Jr.*, 1932, xxxix, 601.
7. HOLMES, GORDON: Acute febrile polyneuritis, *Brit. Med. Jr.*, 1917, ii, 37.
8. BRADFORD, J. R., BASHFORD, E. F., and WILSON, J. A.: Acute infective polyneuritis, *Quart. Jr. Med.*, 1918, xii, 88.
9. CASAMAJOR, LOUIS: Acute ascending paralysis among troops: pathologic findings, *Arch. Neurol. and Psychiat.*, 1919, ii, 605.
10. KENNEDY, F.: Infective neuronitis, *Arch. Neurol. and Psychiat.*, 1919, ii, 621.
11. MACKAY, ROLAND P.: Acute encephalo-myelo-radiculoneuritis (Guillain-Barré syndrome), *Med. Clin. N. Am.*, 1945, 1-8.
12. LASSEN, H. C. A., IPSEN, J., and BANG, J.: Etiological studies on acute polyradiculitis of the Landry type—experiments on the demonstration of a virus with negative outcome, *Acta med. Scand.*, 1943, cxv, 193.
13. LEWEY, F. H.: What is the Guillain Barré syndrome? A study of the underlying pathological lesions, *Jr. Pediat.*, 1945, i, 166.
14. LOWENBERG, K., and FOSTER, D. B.: Polyradiculoneuritis with albuminocytologic dissociation; patho-anatomic report of 3 cases, *Arch. Neurol. and Psychiat.*, 1945, liii, 185-190.
15. DEJONG, R. N.: The Guillain Barré syndrome—polyradiculitis with albumino cytologic dissociation, *Arch. Neurol. and Psychiat.*, 1940, xlv, 1068.
16. Report of the Matheson Commission—Epidemic encephalitis, etiology, epidemiology, treatment, 1939, Columbia University Press, New York, pp. 44-47.
17. BARKER, L. F., CROSS, E. S., and IRWIN, S. V.: On the epidemic acute and subacute non-suppurative inflammations of the nervous system prevalent in the United States in 1918-1919—encephalitis, encephalomyelitis, polyneuritis and meningo-encephalitis, *Am. Jr. Med. Sci.*, 1920, clxx, 157.
18. BERTEL, L., and DEVIC, A.: Les formes "périphériques" de l'encephalite epidemique, *Presse méd.*, 1925, xxxiii, 1441.
19. BARRÉ, J. A.: Considérations diverse sur le syndrome de polyradiculonervite avec dissociation albumino-cytologique, *Jr. Belge de Neurol. et de Psychiat.*, 1938, xxxviii, 313.
20. HECHT, M. S.: Acute infective polyneuritis in childhood, *Jr. Pediat.*, 1937, xi, 743.
21. TAYLOR, E. W., and McDONALD, C. A.: The syndrome of polyneuritis with facial diplegia, *Arch. Neurol. and Psychiat.*, 1942, xxvii, 79.
22. GILPIN, S. F., MOERSCH, F. P., and KERNOHAN, J. W.: Polyneuritis, a clinical and pathological study of a special group of cases frequently referred to as instances of neuronitis, *Arch. Neurol. and Psychiat.*, 1936, xxxv, 937.
23. BARKER, L. F.: Acute diffuse (cerebral and spinal) polyradiculoneuritis following oral sepsis, *Arch. Neurol. and Psychiat.*, 1934, xxxi, 837.
24. ALAJUANINE, T., THUREL, R., HORNET, T., and BOUDIN, G.: La polyradiculonervite aigue généralisée avec diplégie faciale et paralysie terminale des muscles respiratoires et avec dissociation albumino-cytologique, *Rev. Neurol. and Psychiat.*, 1936, i, 681.
25. STRAUS, J., and RABINER, A. M.: Myeloradiculitis—A clinical report of 7 cases, *Arch. Neurol. and Psychiat.*, 1930, xxiii, 40.

# MENINGITIS DUE TO *PSEUDOMONAS PYOCYANEA*: A REPORT OF THREE CASES TREATED SUCCESSFULLY WITH STREPTOMYCIN AND SULFADIAZINE \*

By LOUIS WEINSTEIN and THOMAS S. PERRIN, *Boston, Massachusetts*

INFECTIONS of the meninges with *Pseudomonas pyocyanea* (*Pseudomonas aeruginosa*) are distinctly uncommon but cannot be dismissed as unimportant because they have a high mortality rate, and constitute a serious risk in any procedure involving penetration of the membranes surrounding the brain or spinal cord. Stanley,<sup>1</sup> in a recent review of the literature, collected 41 cases of primary *Ps. pyocyanea* meningitis and 28 additional instances in which this disease appeared to be secondary to a focus elsewhere. To the latter type he added one case of his own. Of the group of primary meningitides, 78 per cent occurred as a result of the introduction of organisms during spinal puncture for diagnostic purposes or the instillation of contaminated anesthetic or other drug solutions into the subarachnoid space. Four individuals in whom this type of meningeal infection occurred during the course of intrathecal penicillin therapy for pneumococcal meningitis have been described by Harris et al.<sup>2</sup> Cairns and his co-workers have added descriptions of three more instances of meningitis due to this organism to the literature and Merwarth et al.<sup>4</sup> have contributed another. Three patients with *Ps. pyocyanea* meningitis were studied by Paine et al.<sup>5,6</sup> and another case has been reported by DeBakey and Pulaski.<sup>7</sup> There are in the literature, therefore, a total of at least 82 reported instances of infection of the meninges with *Ps. pyocyanea*.

Treatment of *Ps. pyocyanea* has been uncertain and, on the whole, unsatisfactory. Harris et al. have reviewed the results of the use of sulfonamides and penicillin in this disease and found that of 21 cases treated with these drugs 15 (71.5 per cent) died.

Streptomycin has been shown to be inhibitory for *Ps. pyocyanea* in concentrations varying from 2 to 200 micrograms per ml. Most strains fail to grow in 8 to 50 micrograms per ml,<sup>8</sup> however, and, therefore, are susceptible to levels of this drug which are obtainable in the spinal fluid with generally accepted intrathecal doses.

A total of nine cases of *Ps. pyocyanea* meningitis treated with streptomycin have been reported in the literature (table 1). Of this group five died, a mortality rate of 55.5 per cent. The first case reported by Paine et al. (Case 1) was given intramuscular and intrathecal penicillin and oral

\* Received for publication November 4, 1947.

From the Haynes Memorial and Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

TABLE I  
Meningitis Due to *B. pyocyaneus*, Streptomycin Treated

Case No.	Author	Age	Primary Condition	Presumed Mode of Infection	Amount of Single Dose of Streptomycin	Total Dose of Streptomycin	Additional Treatment	Course of the Disease	Outcome
1	Paine et al.	14	Epileptic seizure	Lumbar puncture	IT = 0.05 gm. IM = 1.0 gm.	IT = 0.45 gm. IM = 28 gm.	Sulfadiazine and IM penicillin	Rapid improvement	Recovered
2	Paine et al.	11 days	Congenital meningococle	Débridement of meningococle	IV = 0.25 gm.	IV = .55 gm. IM = 6.5 gm.	Penicillin IM and IT	Gradual improvement	Recovered
3	Paine and Finland	?	?	?	?	?	?	?	Died
4	Cairns et al.	?	Lateral sinus thrombosis, cerebral and cerebellar abscess	Cerebellar decomposition	IV = 80,000 units	IV = 620,000 units	Sulfonamides, penicillin	Unaffected	Died
5	Cairns et al.	?	Gunshot wound of neck	Wound infection	IV = 100,000 units IT = 100,000 units	IV = 210,000 units IT = 100,000 units	Sulfonamides, penicillin	Unaffected	Died
6	Cairns et al.	?	?	?	IT = 100,000 units	IT = 100,000 units	Sulfonamides	Rapid deterioration	Died in 7½ days
7	Merwarth et al.	23	Meningococcal meningitis	?	IT = 50,000-100,000 units IM = 1 gm.	IT = 500,000 units IM = 14.5 gm.	Sulfadiazine	Rapid improvement	Recovered
8	DeBakey and Pulaski	?	?	?	?	?	?	?	Recovered
9	Stanley	17	Chronic disseminated lupus erythematosus	<i>B. pyocyaneus</i> septicemia, with terminal meningitis	SC = 250,000 units-500,000 units	SC = 5,810,000 units	-----	Transitory improvement	Died

IT = intrathecal; IV = intraventricular; IM = intramuscular; SC = subcutaneous

sulfadiazine for four days without any beneficial effect before therapy with streptomycin was started; the antibiotic agent produced rapid improvement and complete recovery. The second case described by these authors (Case 2) was 11 days of age and received four days of ineffective penicillin therapy (intramuscular and intrathecal) before streptomycin was started three days later. The use of this drug led to gradual improvement but there was evidence of residual central nervous system damage. The neurological sequelae may have been due to the greater virulence of the organism and the delay in treatment. Case 3 was not reported in detail but the strain of *Ps. pyocyanea* recovered from the spinal fluid became totally resistant to streptomycin during treatment and the patient died. Three patients, all of whom died, were reported by Cairns and his co-workers (Cases 4, 5, 6). The first two individuals were first treated with streptomycin, penicillin, and sulfadiazine 10 days after the onset of their disease, by which time each had apparently developed a block at some point in the cerebrospinal pathway. The third case was not reported in detail; the subject is said to have been severely ill but not moribund at the time of his first injection but died 7½ hours after treatment was begun.

The patient reported by Merwarth, et al. (Case 7) was a young woman who developed *Ps. pyocyanea* meningitis following intrathecal administration of penicillin for meningococcal meningitis. Improvement was dramatic after the exhibition of streptomycin, but three weeks after discontinuation of treatment, a lower motor neuron lesion affecting all four extremities developed; this regressed partially during the next eight months. The neurological sequela was attributed by the authors to a neuro-toxic reaction caused by the streptomycin. A case of *pyocyanea* meningitis (Case 8) successfully treated with streptomycin was described by DeBakey and Pulaski; no details were given. The patient reported by Stanley (Case 9) developed *Ps. pyocyanea* bacteremia during the last stages of disseminated lupus erythematosus. Subcutaneous administration of streptomycin was begun shortly after the diagnosis was established and continued until death about 60 hours later. Meningitis was discovered at necropsy and was presumed to be due to *Ps. pyocyanea* although the meningeal exudate was not cultured. No intrathecal streptomycin was given.

It is the purpose of this report to present three cases of meningitis due to *Ps. pyocyanea* occurring after administration of a spinal anesthetic. All of the patients were treated with streptomycin and sulfonamide and recovered.

*Case 1.* The patient, a 16 year old white male high school student, was referred to the John C. Haynes Memorial Hospital from another hospital because of meningitis. Nine days before admission here he underwent an appendectomy for recurrent bouts of lower abdominal pain. Anesthesia was produced by the intraspinal injection of pontocaine-glucose solution. Two days postoperatively a severe headache and a rise in temperature developed. Penicillin was administered intramuscularly but fever and headache persisted, the neck became stiff, and a positive Kernig's sign became apparent. Three days before admission lumbar puncture revealed the cerebrospinal



fluid to contain 800 cells (type not determined). Cultures of the fluid grew out *Ps. pyocyanea*. Because of this finding, 0.25 gram of streptomycin was given intramuscularly every three hours for 24 hours. On the day before admission the spinal fluid was found to be cloudy and to contain 2425 cells, of which 90 per cent were polymorphonuclear leukocytes and 10 per cent lymphocytes. The sugar and protein content were within normal limits; a rare gram negative rod was found on gram stained smears. At the time of this lumbar puncture 0.1 gram of streptomycin was injected intrathecally, and the intramuscular dose was increased to 0.5 gram every three hours. Culture of the fluid again yielded *Ps. pyocyanea*. This strain was found to be sensitive to 7.8 units of streptomycin per c.c.

On admission to the Haynes Memorial Hospital the patient appeared mildly ill and complained only of headache. The temperature was 101° F., the pulse 78, the respirations 24, and the blood pressure 122 mm. Hg systolic and 70 mm. diastolic. Physical examination was negative except for moderate stiffness of the neck and weakly positive Kernig's sign bilaterally. Lumbar puncture revealed an initial pressure of 250 mm. of spinal fluid, 396 cells, of which 83 per cent were neutrophils and the remainder lymphocytes. An occasional gram negative rod was seen on smear, but no organisms were obtained on culture. Total protein was 83 mg. and sugar 70 mg. per 100 c.c. The peripheral white blood count was 13,900, with 78 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes, and 4 per cent monocytes. The urine was not remarkable.

The patient was continued on the intramuscular schedule of streptomycin begun before transfer and given 0.1 mg. of the drug intrathecally every 24 hours, in addition. He continued to maintain an irregular elevation of temperature which never exceeded 102.6° rectally, however. Headache disappeared overnight, and the stiffness of the neck became less marked. By the fourth hospital day the cerebrospinal fluid cell count, which had fallen each day, had decreased to a total of 45 per cu. mm., of which 90 per cent were lymphocytes; no organisms had been seen in gram stained smears or recovered on culture. On the fourth hospital day the intramuscular streptomycin was discontinued and three days later the intrathecal use of the drug was halted; at this time the spinal fluid contained 180 cells, of which 90 per cent were lymphocytes; cultures of the spinal fluid remained negative.

Coincident with the cessation of intraspinal streptomycin therapy, the temperature, which had been slightly elevated, fell to essentially normal levels and remained so for three days. During this period the patient felt well, had a supple neck, the Kernig's signs were negative, and he was allowed up in a chair. On the fourth day after treatment was stopped, the temperature rose to 101° and a mild headache was present. The neck remained supple, and the Kernig's signs were negative. Lumbar puncture yielded a cloudy fluid containing 1340 white blood cells, of which 84 per cent were neutrophils. No organisms were seen on smear or recovered on culture. Because of these findings, the patient was started on a regimen of 0.1 gram of streptomycin intrathecally and 4 grams of the same drug intramuscularly every 24 hours. In addition he was given an initial dose of 4 grams of sulfadiazine, followed by 1 gram every four hours thereafter.

The headache disappeared within 24 hours and the temperature rapidly returned to normal levels. The cell count of the spinal fluid decreased so that after eight days of therapy only 20 lymphocytes per cu. mm. were present. After about four days of treatment, occasional episodes of vomiting, with little or no nausea, began to occur. Intramuscular streptomycin was stopped after six days but the intrathecal administration of the drug was continued. Three days later, because of persistent vomiting, sulfadiazine was discontinued, and sulfamerazine, 1 gram every 8 hours intravenously, substituted. The neck was still slightly stiff, and the Kernig's weakly positive. Streptomycin treatment was discontinued after the intraspinal injection on this day.

Vomiting ceased the next day and it was possible to give the sulfamerazine by mouth. Thirteen days after reinstitution of therapy, five days without streptomycin, the patient was asymptomatic and lumbar puncture revealed a clear spinal fluid containing only three lymphocytes per cu. mm. Moderate stiffness of the neck and weakly positive Kernig's sign persisted, however. After 12 days of normal temperature while on sulfamerazine therapy alone, the patient had a rise in temperature to 101° but felt entirely well. The sulfonamide was stopped at this time.

After three days without any treatment, a lumbar puncture was performed because of persistent low grade fever, and yielded a slightly cloudy fluid containing 2220 cells per cu. mm., of which 86 per cent were neutrophiles; no organisms were seen on smear or recovered on culture. The patient had no complaints at this time and the only positive physical findings were slight stiffness of the neck and slightly positive Kernig's signs. Intrathecal and intramuscular streptomycin (0.1 and 4 grams respectively per 24 hours) and sulfamerazine orally (6 grams per day) were exhibited again on this day. There was again a rapid progressive decrease in spinal fluid cell count; seven days after treatment was instituted there were only 20 cells, 90 per cent lymphocytes, per cu. mm. The temperature gradually declined to normal levels but rose again on the seventh day of treatment to 101.8°. At this time pain, tenderness, redness, heat, and induration were noted at the sites of injection of streptomycin in both buttocks. Because the elevation of temperature was thought to be due to these local infections and the spinal fluid was essentially normal, intramuscular streptomycin was discontinued on the ninth day of therapy. The temperature returned to normal within 48 hours. Despite laboratory evidence of improvement, the patient's neck and back were stiff, and the Kernig's signs remained positive. Intrathecal administration of streptomycin was stopped after 15 days but sulfamerazine was continued for seven days longer. The spasm of the neck and back muscles gradually decreased.

Two days after all medication had been discontinued, the temperature rose to 101.2°, and pain and stiffness of the neck were present; the Kernig's sign was positive. Neurological examination was otherwise normal and there was no tenderness to heavy percussion over the spine. Lumbar puncture revealed a xanthochromic spinal fluid containing many red blood cells and 5800 white cells, of which 95 per cent were neutrophiles. No organisms were seen on gram stained smears or obtained on culture. Cerebrospinal fluid obtained a few hours later, however, yielded *Ps. pyocyanea*.

Since all the treatment given previously had failed, a trial of large doses of intrathecal penicillin (50,000 units every 12 hours) was decided upon. After four days, when it had been found that the organisms were resistant to 500 units of penicillin per c.c., this drug was stopped. Sulfamerazine therapy was again initiated at this time and continued for four days, following which sulfadiazine was substituted for it and the dose increased so that the patient received 14.5 grams the first day and 12 grams a day thereafter. Studies of the sulfadiazine resistance of the strain of *Ps. pyocyanea* which had been isolated showed that it was inhibited by 25 but not by 5 mg. per 100 c.c. of this drug. Since only 4-5 mg. of sulfonamide per 100 c.c. of spinal fluid had been present on the dosage of sulfadiazine previously employed, about  $\frac{1}{3}$  of the blood level, it was thought necessary to administer large amounts of the sulfonamide in order to produce an effective spinal fluid level. There was clinical improvement on this regimen and the spinal fluid cell count fell to 104 per cu. mm. in three days. However, six days after the initiation of massive sulfadiazine therapy the temperature rose to 102.2° and there was again pain in the neck. A lumbar puncture revealed 5000 white blood cells, and *Ps. pyocyanea* was still present. Since the organism isolated at the beginning of the present relapse was found to be sensitive to a concentration of 15 units of streptomycin per c.c., this drug was administered intrathecally, 0.1 gram every 24 hours, in addition to the sulfadiazine.

The temperature returned gradually to normal, and the pain in the neck dis-

appeared. The number of cells in the spinal fluid also began to decline. After seven days of intrathecal streptomycin therapy, the intramuscular injection of this drug, 4 grams per day, was added. At about this time the back and neck began to grow very stiff, and hot wet packs were applied, with amelioration of symptoms. All chemotherapy was stopped after the patient had received sulfadiazine for four weeks, intrathecal streptomycin for three weeks, and intramuscular streptomycin for two weeks.

The patient was gotten out of bed and seemed to be feeling well. He remained afebrile but eight days after cessation of treatment vomited several times and complained of slight pain and stiffness in the back of the neck. Although the temperature at this time was normal, a lumbar puncture yielded xanthochromic, bloody spinal fluid which contained 5350 white blood cells per cu. mm. No bacteria could be demonstrated. Intrathecal and intramuscular streptomycin, as well as sulfadiazine, was again administered in the same dosage as in the preceding relapse. Intermittent vomiting and an almost constant complaint of frontal and occipital headache and pain and stiffness of the neck were present. Intravenous hydration and the administration of sulfonamide by vein were necessary frequently. The nuchal discomfort was considerably benefited by hot packs. In order to reduce the frequency of parenteral medication, sulfadiazine was replaced by sulfamerazine, the dose of the latter being 2 grams every eight hours. Vomiting subsided gradually and the other symptoms gradually abated; within a week the spinal fluid cleared remarkably and contained 0 to 10 cells per cu. mm. After four weeks of treatment with streptomycin (intrathecal and intramuscular) and sulfonamides, all medication was stopped.

During the last course of chemotherapy, the patient's hearing, which had been normal for conversational tones, began to fail and he became quite deaf, though never totally so. The deafness seemed to increase somewhat for several days after streptomycin was discontinued and then gradually improved, but was still present in moderate degree at the time of dismissal from the hospital. The stiffness of the neck varied somewhat, and was marked at the time of discontinuance of chemotherapy but began to improve very rapidly after a few days.

Twenty-seven days after cessation of treatment the patient was discharged from the hospital. He had remained afebrile during this time and his neck had become almost normally supple, but slight stiffness of the back still persisted. He had been up in a wheel chair for some time and was able to walk short distances without support. A follow-up visit a month after leaving the hospital revealed complete recovery without any sequelae except for bilateral partial deafness.

The patient received a total of 8.1 grams of streptomycin intrathecally, and 227 grams intramuscularly during the entire course of treatment.

*Case 2.* The patient was a 58 year old white female who was admitted to the John C. Haynes Memorial Hospital with a diagnosis of meningitis. Four days before admission she had undergone an operation at another hospital for repair of a cystocele and rectocele, anesthesia being produced by the intrathecal injection of procaine solution. On the first postoperative day there was a headache and a rise in temperature. The fever increased, cephalalgia became progressively more severe, and stiffness of the neck became apparent. Three days after operation a lumbar puncture yielded a fluid containing about 4000 cells, all of which were said to be neutrophils and the patient was sent to the Haynes Memorial the next day. The past history was of significance only in that diabetes had been present for about five years; this was controlled by 16 units of protamine zinc insulin daily and a rather casually followed diet.

The only remarkable findings on physical examination at the time of admission were marked stiffness of the neck, bilaterally positive Kernig's sign, and the evidence of the recent operation, which appeared to be healing normally. Lumbar puncture revealed a pressure of 210 mm. and cloudy spinal fluid containing 3860 cells of which

72 per cent were neutrophils and 28 per cent lymphocytes; the total protein was 104 mg. and the sugar 34 mg. per 100 c.c. Gram negative rods were seen on smear, and *Ps. pyocyanea* was recovered on culture; the strain was found to be sensitive to 31.5 units of streptomycin per c.c. The urine was free of sugar and ketones and was otherwise not remarkable.

On the day of admission, the patient was placed on a regimen of 0.1 gram of streptomycin intrathecally every 24 hours as well as 0.5 gram of this drug intramuscularly every three hours. For the first three days there was some improvement, with decrease in headache and fall in temperature; on this day the number of cells in the spinal fluid was 810 per cu. mm., of which 82 per cent were neutrophils and the remainder lymphocytes. No organisms had been demonstrated in smears or cultures of the spinal fluid since the beginning of treatment. On the next day, however, headache was worse, the temperature rose, and the patient felt very ill again. Lumbar puncture revealed 3000 white blood cells, and gram negative bacilli. Because of these findings the intrathecal injections of streptomycin were increased to twice daily (0.1

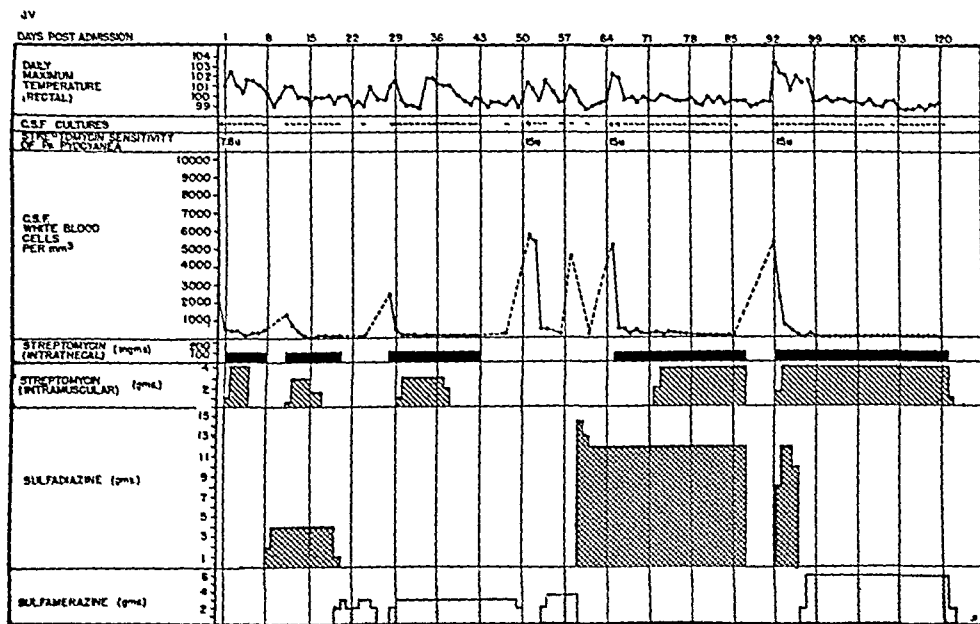


CHART 1.

gram every 12 hours) and sulfadiazine (initial dose of 4 grams, followed by 1 gram every four hours orally) was given in addition. The intramuscular administration of streptomycin was continued as before. The general clinical condition improved rapidly; the headache disappeared and the temperature fell to a normal level in 36 hours. Stiffness of the neck had entirely disappeared seven days after admission. On the evening of the seventh day the patient developed a marked vertical nystagmus and complained of a sensation of "going over a waterfall." Intramuscular streptomycin was discontinued because of these findings and the nystagmus and vertigo disappeared overnight. There was no tinnitus or deafness.

The intrathecal injection of streptomycin was discontinued after 12 days. At this time the spinal fluid contained only 180 cells per cu. mm., of which the great majority were lymphocytes; total protein was 131.6 mg. per 100 c.c., the chloride level was 121.5 m. eq., and the sugar content was normal.

Sulfadiazine was continued through the eighteenth hospital day, the patient remaining symptomatically well and afebrile. On the eighteenth day, there were only

46 white blood cells per cu. mm. of spinal fluid; 91 per cent were lymphocytes. The spinal fluid total protein was decreased to 80 mg. per 100 c.c. and no organisms were seen on smear or recovered on culture.

The patient was allowed out of bed and seemed to be convalescing uneventfully, when on the twenty-third day she had a sudden onset of pain and swelling of the left leg, with tenderness over the calf. A diagnosis of left femoral-iliac phlebothrombosis was made, and at operation a clot was evacuated from the left femoral and iliac veins. The veins of the left leg were ligated but those on the right were not closed because the patient went into shock during operation. Heparin was given for 48 hours post-operatively and then dicoumarol for the next 29 days, the prothrombin time being maintained at an adequate level. The swelling and pain in the affected leg subsided gradually and there was no evidence of further phlebothrombosis or pulmonary infarction.

By the thirty-ninth day the patient was up again in a chair and was free from any difficulty except swelling of the left lower extremity. Shortly after this time she began to complain bitterly of shooting, cramping pain in the lumbo-sacral region which required opiates for relief. No explanation for the pain could be found on physical or roentgenologic examination. Because of the possibility of diabetic neuritis, large doses of the vitamin B complex were given parenterally but the pain persisted and was aggravated by motion to such a degree that there was great reluctance to walk.

Thirty-two days after the discontinuance of all therapy, the temperature suddenly rose to 102° (R). The patient had no complaints other than the persistent pain in the lumbo-sacral region, but the neck was slightly stiff. The spinal fluid contained 6000 white cells per cu. mm., with 80 per cent neutrophils and 20 per cent lymphocytes, and *Ps. pyocyanea* was obtained on culture. Sulfadiazine, five grams initially followed by 1 gram every four hours, was administered. The temperature returned to normal within 48 hours and the stiffness of the neck disappeared. When the spinal fluid was examined on the third day after the recurrence, it revealed 204 white blood cells, of which 99 per cent were lymphocytes. *Ps. pyocyanea* was recovered in cultures and the strain proved to be sensitive to 30 units of streptomycin per c.c. and to more than 5 but less than 25 mg. of sulfadiazine per 100 c.c. Intrathecal streptomycin injections, 100 mg. every 24 hours, were resumed one week after the recurrence of the meningitis; at this time the spinal fluid contained only 18 lymphocytes per cu. mm. but the Gram negative bacteria were still present. Within the next 24 hours, the temperature, which had been normal, rose to 101.8° (R), with no appreciable change in physical findings; the spinal fluid contained 13,830 white cells per cu. mm. (52 per cent lymphocytes and 38 per cent neutrophils) and *Ps. pyocyanea*. The fever abated during the next day and there was a rapid fall in the number of cells in the spinal fluid. No organisms were present in this or any of the subsequent spinal fluid cultures. Intramuscular streptomycin (4 grams per day) was added to the other therapy on the fourteenth day of the recurrence of meningitis. At this time vomiting appeared and persisted for several days and the patient began to complain of difficulty in hearing conversational tones.

Twenty-three days after resumption of intrathecal treatment, a series of generalized convulsions, lasting about an hour occurred, and was followed by stupor. A lumbar puncture revealed 550 red cells and 550 white blood cells per cu. mm. (91 per cent lymphocytes). There were no localizing neurological signs or paralysis. Within 24 hours consciousness returned but the patient was euphoric and had some difficulty in recognizing people. Intrathecal streptomycin was discontinued immediately after the convulsive episode and the intramuscular drug as well as sulfadiazine was omitted five days later. Severe cramping pains in the buttocks appeared at about this time and persisted until discharge. An epidural injection of procaine

(1 per cent) at the junction of the sacrum and coccyx, followed by the instillation of 100 c.c. of saline, produced only transitory relief of the discomfort. The deafness, which was more severe in the right than the left ear, also persisted and, although moderately severe, was not complete.

The patient gradually became ambulatory, remained afebrile, and was free of any sign of meningeal irritation. The lumbar, sacral, and buttock pain waxed and waned in severity but frequently could be relieved by 0.3 gram of acetylsalicylic and/or by placebos. The euphoria noted immediately after the episode of convulsions gave way to alternating periods of depression and elation.

In this condition the patient was discharged from the hospital 111 days after admission. Follow-up reports during the next six weeks revealed persistence of the pain in the back with resultant difficulty in walking. An arachnoiditis was presumed to be the cause of the severe lumbo-sacral discomfort. During the entire course of treatment, a total of 2.9 grams of streptomycin had been administered intrathecally and 83 grams given intramuscularly.

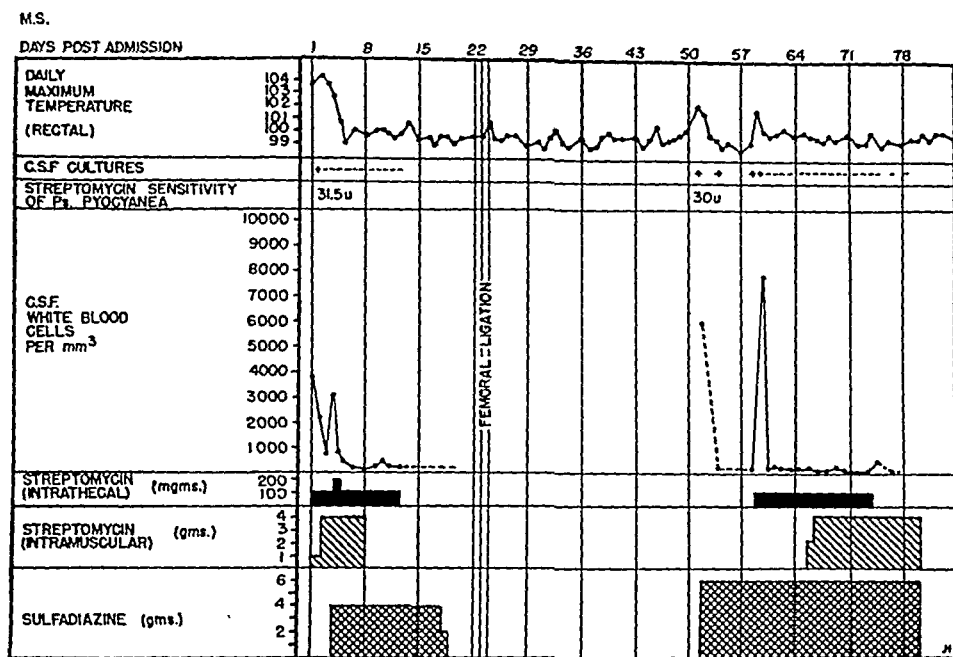


CHART 2.

*Case 3.* The patient was a 33 year old white married woman who was subjected to appendectomy under a spinal anesthesia with pontocaine-glucose solution. She remained in the hospital for 12 days after operation, and was quite well except for occasional pain in the flanks and a mild headache. Soon after returning home, she began to have generalized malaise, a constant throbbing headache, stiffness of the neck, and fever ranging from 101°-102° F. The headache grew steadily worse and vertigo, tinnitus, and paresthesias of both arms developed.

Nineteen days after operation, the patient was admitted to the Haynes Memorial Hospital with a diagnosis of meningitis. Physical examination on admission revealed stiffness of the neck and back, a healing right lower quadrant scar, negative Kernig's signs, and brisk, equal deep tendon reflexes. There was slight papilledema and moderate engorgement of the retinal veins bilaterally. The temperature was 100.6° F. The cerebrospinal fluid was under a pressure of 250 mm. and contained 1656 white

blood cells per cu. mm. (66 per cent neutrophils and 34 per cent lymphocytes); the sugar was 61 mg. and the total protein was 75.2 mg. per 100 c.c. An occasional gram negative rod was seen on examination of spun sediment, and *Ps. pyocyanea* was obtained on culture. The peripheral white blood count was 10,600, with 95 per cent neutrophils and 5 per cent lymphocytes. The strain of *Pseudomonas* was sensitive to 15 units of streptomycin per c.c.

Streptomycin, 0.1 gram intrathecally and 4 grams intramuscularly, as well as 6 grams of sulfadiazine, was administered every 24 hours as soon as the diagnosis was established. The headache improved rapidly and disappeared within 24 hours. Because of difficulty in voiding urine, a Foley catheter was inserted and left in place. Urinary output was adequate until the morning of the fourth hospital day when for a period of 14 hours only about 10 c.c. of extremely bloody fluid was passed through the catheter. Administration of sulfonamide and intramuscular streptomycin was stopped within two hours of the time of cessation of urine output, after it had been established that the catheter was patent, and a moderate amount of fluid was given intravenously. After 14 hours the urine flow was reestablished and 3750 c.c. were voided in the next 12 hours. At this time, intramuscular streptomycin therapy was started again and six days later sulfamerazine (2 grams initially followed by 1 gram every eight hours) was added. There was no further episode of anuria or oliguria, although microscopic hematuria was present for about six days. The Foley catheter was removed on the ninth hospital day, and normal micturition took place thereafter.

During the next few weeks the patient complained frequently of prickling sensations on the face, and over the extremities and, on one occasion, showed extensor spasm of the legs and left arm. She developed back pain, centering about the site of the injections; this disappeared rapidly after a reassuring conversation. Pain and paresthesias in the legs and thighs occurred sporadically. Five weeks after admission to the hospital the knee and ankle jerks on both sides disappeared completely and had not returned at the time of discharge. Pain and light touch sensation and position sense remained intact. Tinnitus began to appear and progressed until it was constant. Deafness, which was first noted about the eleventh day of treatment, progressed rapidly until it became almost total. Intramuscular streptomycin was discontinued on the thirteenth day, and some increase in hearing became apparent within 48 hours, but improvement thereafter was very slow. Stiffness of the back and neck disappeared quite slowly.

*Ps. pyocyanea* was not recovered in cultures of the cerebrospinal fluid after the first lumbar puncture, although attempts to grow the organisms were made daily for 18 days. The number of white cells in the spinal fluid decreased to 192 per cu. mm., with a preponderance of lymphocytes, after one week of treatment. Intrathecal streptomycin was discontinued on the eighteenth hospital day.

The patient was allowed to sit in a chair in the sixth week and soon thereafter attempts were made to induce her to walk. It was apparent that marked incoördination of muscles of the lower extremities was present. The Romberg test was positive, but not lateralized. Caloric stimulation of the vestibular apparatus was attempted on three occasions, without production of nystagmus, past pointing, vertigo, or falling to either side. No other sensory impairment occurred during the course of the illness. Massage and active and passive exercises were carried out and gradually the patient learned to walk without help but only with her eyes open.

Sulfamerazine was discontinued on the twenty-seventh hospital day. One week later the cerebrospinal fluid contained only 26 cells per cu. mm., of which 92 per cent were lymphocytes; the total protein remained elevated to 186 mg. per 100 c.c.

The patient ran a low grade, irregular fever (100°–101.2° F.) constantly for the first 13 days of her hospital stay. After discontinuing intramuscular streptomycin, the temperature returned to normal and remained so during the rest of the hospital

stay. During the six weeks following cessation of all chemotherapy (the entire course is not depicted in chart 3), stiffness of the neck and back entirely disappeared. Hearing improved gradually, so that at the end of the period the patient could understand loud conversation. Tinnitus, described as "bells" or "crackling of paper" superimposed on a low pitched "droning," continued sporadically, but seemed progressively less severe.

A total of 1.8 grams of streptomycin was administered intrathecally and 36.5 grams given intramuscularly during the course of treatment. A follow-up examination six weeks after discharge from the hospital revealed the patient to be quite well. She still complained of tinnitus and deafness was moderate, but she was able to walk well except in the dark.

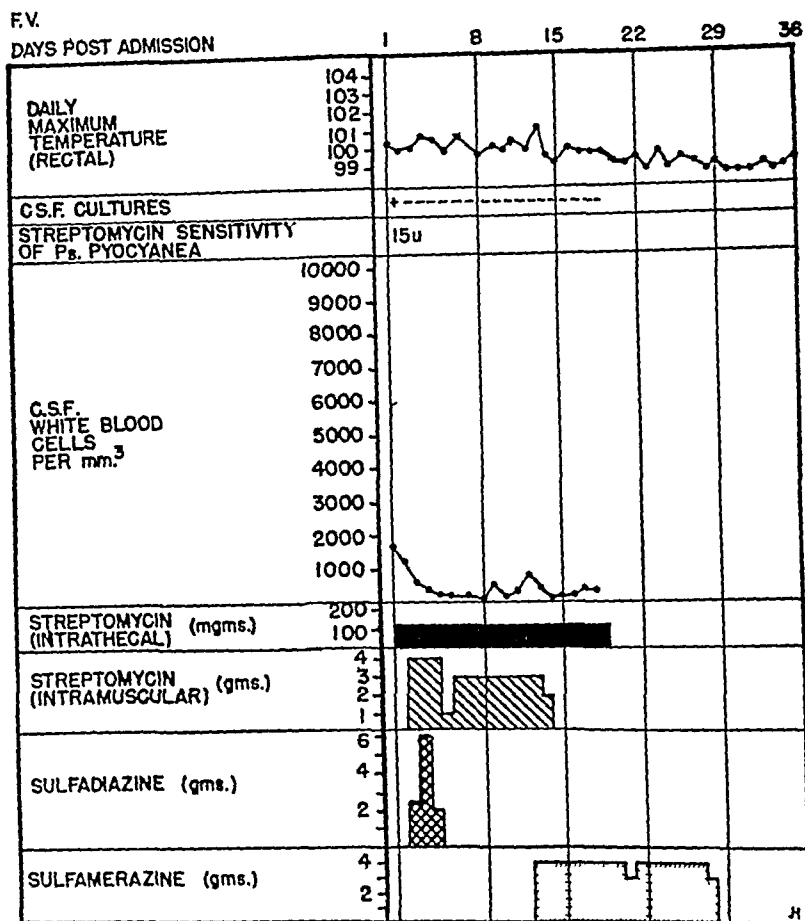


CHART 3.

## DISCUSSION

In the light of the previously recorded observations that the majority of primary meningitides due to *Ps. pyocyanea* results from the introduction of the organisms during the course of spinal or cisternal punctures for diagnostic or therapeutic purposes, it is important to emphasize the fact that all three of the cases reported in this paper followed the instillation of a spinal



anesthetic; in two instances pontocaine-glucose solution was used and in the third, procaine was injected. All of the cases occurred in the same hospital during a 13 day-period and were treated by the same anesthetist; no other cases of this type were seen in this hospital subsequently. No information could be obtained concerning the source of the organisms which were found in the spinal fluid, since none of the solutions used were available for bacteriologic examination; it must be presumed, however, that they were introduced at the time of production of spinal anesthesia. Careful check of the sterilization procedures revealed no errors which might have allowed contamination of the instruments used during the production of the spinal anesthesia. Cultures of the skins of the affected individuals did not reveal the causative bacteria. The possibility that *Ps. pyocyanea* may have been present in the materials introduced intrathecally is a very good one since it has been shown that this organism not infrequently contaminates solutions of boric acid, procaine, fluorescein, etc.<sup>1</sup>

An outstanding finding in the treatment of these cases was the rapid response to combined streptomycin and sulfonamide therapy. The protracted course of the first of these patients offered an unusual opportunity to assess crudely the relative merits of streptomycin and sulfonamide, alone and in combination. Whenever streptomycin was administered by the intrathecal and intramuscular routes, alone or together with sulfonamide, the patient's symptoms tended to abate, the temperature returned towards normal, the spinal fluid, if infected with *Ps. pyocyanea*, became sterile within 48 hours, and the number of white blood cells in the fluid declined towards normal. Penicillin intrathecally was given a brief trial but was singularly ineffective. Sulfonamide, used alone, also failed to control the meningeal infection, although temporary amelioration of the severity of the disease was produced by large doses of this drug; 12 grams of sulfadiazine per day produced moderate improvement for only a period of about six days. It would appear, therefore, that treatment with streptomycin is the sine qua non of successful therapy of primary meningitis due to *Ps. pyocyanea*. That caution must be exercised in considering a patient cured of the disease is indicated by the course of events in case 2, in whom a recurrence, with repeatedly positive spinal fluid cultures occurred 32 days after all therapy had been discontinued.

Although *Ps. pyocyanea* is considered to be one of the organisms in which resistance to streptomycin develops with great ease<sup>6, 9</sup> it is noteworthy that in none of the cases reported here did the causative bacteria show any tendency to become resistant. In both patients in whom relapses occurred, the strains isolated at various times during the course of the disease showed no essential change in sensitivity to streptomycin. In case 1, during four recurrences, the organism was sensitive to 7.8 to 15 units of the drug per c.c., while in case 2, the bacteria isolated 32 days after cessation of treatment were no more resistant than they were before being exposed to the antibiotic agent.

The important complications which occurred during the course of treatment were the result of involvement of the eighth cranial nerve. All of the patients developed a marked degree of deafness during therapy. In case 3, loss of hearing appeared in the first week in the hospital, shortly after the inception of streptomycin administration. This patient had tinnitus prior to admission but this subsided during the first few days of hospitalization and she did not complain of it again until after the onset of deafness. In the other two cases clinically apparent deafness developed only after re-institution of streptomycin treatment because of a relapse of the disease. There was improvement in hearing of all of the patients following discontinuation of antibiotic therapy. Because of the hopeless outlook of the disease without streptomycin treatment, all patients continued to receive the drug after impairment of hearing became obvious. The specific rôles played by the meningitis and the streptomycin in the production of the deafness cannot be evaluated with certainty.

Disturbance of the vestibular apparatus appeared in two of the patients (cases 2 and 3). In case 2, the disturbance was transitory, consisting only of the brief episode of vertigo, accompanied by a gross vertical nystagmus. In case 3 complete bilateral loss of vestibular function occurred without any associated neurological dysfunction except deafness. Despite this impairment the patient learned to walk again and had no difficulty as long as she was able to orient herself in space visually. So good was her compensation, in fact, that when last seen, 97 days after her discharge from the hospital she was resuming her former hobby of fencing.

The transitory episode of anuria which occurred in case 3 is of considerable interest, although no conclusions can be drawn as to its etiology. The patient was receiving both streptomycin and sulfadiazine at the time, but sulfonamide crystalluria was absent and the urine was alkaline at the time of the incident. Streptomycin therapy was reinstituted as soon as urine formation was observed, and sulfamerazine was given subsequently without any further difficulty except for slight albuminuria for nine days after the incident of anuria. The block to urine flow was probably not due to sulfonamide lithiasis with blockage, but it is possible that an acute lower nephron nephrosis, which has been observed with the sulfonamides, occurred. The rapidity with which all of the manifestations cleared and the absence of further difficulty on resumption of sulfonamide administration militates somewhat against a drug nephrosis. Whether or not streptomycin could have been responsible for the sudden anuria cannot be stated. Some evidence has been presented in the literature indicating that this antibiotic agent may cause decrease in urine formation. Streptomycin injection was associated with a decrease in urinary output in two individuals studied by Rutstein et al.,<sup>10</sup> and depression of water diuresis by the same lot of drug was noted by Molitor and co-workers in rats<sup>11</sup>; the material used was a concentrate which was thought to be relatively impure. Madigan et al.<sup>12</sup> also

noted an antidiuretic effect in rats. Hyalin and granular casts have been found in patients receiving crystalline streptomycin.<sup>13</sup> Transient fatty infiltration of the kidneys has been found in monkeys, following administration of streptomycin parenterally.<sup>11</sup> So far as can be determined, however, no case of anuria in man attributable to streptomycin has been reported.

It is interesting to point out that the recurrences of meningitis in cases 1 and 2 were accompanied by the presence of a variable number of red blood cells and occasionally by xanthochromia in the spinal fluid. While the possibility of traumatic lumbar punctures cannot be ruled out, it seems very likely that a true hemorrhagic meningitis was present at these times. *Ps. pyocyanea* is known to produce a hemorrhagic meningitis in swine,<sup>14</sup> and the organisms show a strong tendency to localize in the smaller blood vessels with the production of thrombosis. This, together with the proteolytic action of these bacteria on tissues, may be responsible for bleeding.

### CONCLUSIONS

1. Three cases of primary meningitis due to *Ps. pyocyanea* successfully treated with intrathecal and intramuscular streptomycin and sulfadiazine or sulfamerazine have been described.

2. All of the cases resulted from infection of the meninges during the course of production of spinal anesthesia. The source of the organisms could not be determined.

3. Two patients showed from one to four relapses of the meningeal infection when treatment was stopped.

4. Deafness occurred as a complication in all of the patients and one individual showed severe labyrinthine disturbance with complete loss of vestibular function.

5. Hemorrhagic meningitis may be produced in man by *Ps. pyocyanea*.

6. The strains of *Ps. pyocyanea* responsible for the infections described in this paper were sensitive to between 7.8 and 30 units of streptomycin per c.c. and did not become resistant to the drug during treatment.

7. Streptomycin, in combination with sulfadiazine or sulfamerazine, appears to be the therapy of choice in primary *Ps. pyocyanea* meningitis.

### BIBLIOGRAPHY

1. STANLEY, M. M.: *Bacillus pyocyaneus* infections. A review, report of cases and discussion of newer therapy including streptomycin, Am. Jr. Med., 1947, ii, 253-277, 347-367.
2. HARRIS, R. C., BUNBAUM, L., and APPELBAUM, E.: Secondary *Bacillus pyocyaneus* infection in meningitis following intrathecal penicillin therapy, Jr. Lab. and Clin. Med., 1946, xxxi, 1113-1120.
3. CAIRNS, M., DUTHIE, E. S., and SMITH, H. V.: Intrathecal streptomycin in meningitis. Clinical trial in tuberculous, coliform and other infections, Lancet, 1946, ii, 153-155.
4. MERWARTH, H. R., ROSENBERG, H., and PULITO, F.: *Pyocyaneus* meningitis followed by unusual complications attributed to treatment with streptomycin, Brooklyn Hosp. Jr., 1947, v, 93-96.

5. PAINE, T. F., MURRAY, R., HARRIS, H. W., and FINLAND, M.: Streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system, *Am. Jr. Med. Sci.*, 1947, ccxiii, 676-685.
6. PAINE, T. B., and FINLAND, M.: The use of streptomycin in the treatment of meningitis, *Med. Clin. North Am.*, Boston Number, 1947, 1092-1105.
7. DEBAKEY, M. E., and PULASKI, E. J.: An analysis of the experience with streptomycin in United States Army hospitals. Preliminary report, *Surgery*, 1946, xx, 749-760.
8. MURRAY, R., PAINE, T. F., and FINLAND, M.: Streptomycin. I. Bacteriological and pharmacological aspects, *New England Jr. Med.*, 1947, ccxxxvi, 701-712.
- PAINE, T. F., MURRAY, R., and FINLAND, M.: Streptomycin. II. Clinical uses, *Ibid.*, 1947, ccxxxvi, 748-760.
9. MURRAY, R., KILHAM, L., WILCOX, C., and FINLAND, M.: Development of streptomycin resistance of gram negative bacilli in vitro and during treatment, *Proc. Soc. Exper. Biol. and Med.*, 1946, lxiii, 470-474.
10. RUTSTEIN, D., STEBBINS, R., CATHCART, R., and HARVEY, R.: The absorption and excretion of streptomycin in human chronic typhoid carriers, *Jr. Clin. Invest.*, 1945, xxiv, 898-909.
11. MOLITOR, H., GRAESSLE, O., KUNA, S., MUSHETT, C., and SILBER, R.: Some toxicological and pharmacological properties of streptomycin, *Jr. Pharmacol. and Exper. Therap.*, 1946, lxxxvi, 151-173.
12. MADIGAN, D. G., SWIFT, P. N., and BROWNLEE, G.: Clinical and pharmacologic aspects of toxicity of streptomycin, *Lancet*, 1947, i, 9-11.
13. Committee on Chemotherapeutics and Other Agents. National Research Council. Streptomycin in treatment of infections: Report of one thousand cases, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 4-11, 70-76.
14. KOSKE, F.: Der *Bacillus pyocyaneus* als Erreger einer Rhinitis und Meningitis Hemorrhagica bei Schweinen, *Arb. a. d. k. Gsndhtamt.*, Berlin, 1906, xxxiii, 542-553.

# THE CHALLENGE OF PREVENTIVE MEDICINE \*

By JAMES STEVENS SIMMONS, F.A.C.P., Brig. Gen. U. S. Army, Retired;  
Dean, Harvard School of Public Health

Mr. President, Members of the American College of Physicians, Ladies and Gentlemen:

I appreciate deeply the honor of being asked to give the James D. Bruce Memorial Lecture on Preventive Medicine for 1948. It is a pleasure to attend this Convocation and to be here with so many good friends.

I welcome the opportunity to discuss such a timely subject with this distinguished group of leaders in American Medicine, for I am sure there has never been a period in the history of the country when preventive medicine was of such vital importance to our national welfare and security. We are living in a dangerous age and no one knows where the world is heading; whether toward a firm peace, a continuation of the present armed truce, or another war. Regardless of the answer, the United States will need all of its potential strength—physical, mental and moral—to enable it to meet successfully whatever the future may bring. As physicians, we now face a challenging opportunity for service which is perhaps the greatest ever afforded to any profession; for we are privileged to use our full leadership in the important task of building a healthier, stronger nation.

With this opportunity in mind, I have chosen as the subject of today's talk: "The Challenge of Preventive Medicine." In order to visualize this challenge, it is suggested that we define preventive medicine, trace its development as a constructive factor in national security, estimate its future potentialities, and then consider how we can increase our contribution in this important field.

## DEFINITION

Preventive medicine has the same broad objective as public health; namely, the promotion of individual, community, state and national health. Both specialties are concerned with the prevention of disease and the protection of physical and mental health. As Smillie (1947) has pointed out, however, they may be differentiated on the basis of responsibility. According to him, the term "public health" includes those preventive activities which are recognized as a community responsibility, while the term "preventive medicine" is usually restricted to activities which are the responsibility of the individual. Obviously, these services overlap, but regardless of whether one is dealing with individual preventive medicine, as it is practiced by the family

\*The "James D. Bruce Memorial Lecture on Preventive Medicine for the year 1948," delivered at the Convocation of the American College of Physicians, San Francisco, April 19, 1948.

physician, or with community preventive medicine, as carried out by the specialized profession of public health, the final responsibility for leadership still rests on medicine and its allied professions. Therefore, for the purpose of this discussion, it is suggested that we define preventive medicine as the sum total of all those services required to prevent disease and to keep well people well. Acceptance of this definition implies no decreased appreciation of the importance of curative medicine, but rather adoption of the viewpoint that the entire profession, regardless of specialty, has a responsibility for disease prevention and health promotion.

This concept is not new. It has been preached for years, and it is now practiced faithfully by many physicians and surgeons—particularly the pediatricians and obstetricians. In fact, one of our greatest clinicians, Sir William Osler, made the prediction years ago that “preventive medicine is the medicine of the future. The time has come to ask ourselves how completely we are living up to this broad concept of service and how far we have advanced toward Osler’s vision of the medicine of the future. The answer can be found by reviewing the progress already made, and by making a brief inventory of some of the major health problems which still exist.

#### PAST ACCOMPLISHMENTS

The medical profession of this country can be proud of its past achievements both in curative and preventive medicine. The entire structure of modern medicine has been built within a single century, and much of this progress has occurred during the last 50 years.

The physicians who gathered in Philadelphia on May 7, 1847, to establish the American Medical Association knew nothing about the causes of the infectious diseases with which they worked, and the few pioneer health departments of that day were handicapped by the same universal ignorance. In 1872, when the American Public Health Association was organized by a public-spirited New York physician, Dr. Stephen Smith, the new science of bacteriology was just being born; but health conditions were not much better. The Civil War had been fought without benefit of military preventive medicine and the troops had been ravaged by most of the ancient plagues of war. In that year, the death rates in many American cities exceeded 30 per thousand, the infant mortality ranged from 150 to 200 per thousand live births, and the life expectancy at birth was only about 40 years (Dublin, 1943). Epidemics were common and the United States was frequently invaded by such exotic diseases as Asiatic cholera, European typhus, and yellow fever from the Caribbean.

By the end of the 19th century, information had been discovered about the etiology, diagnosis, transmission and treatment of a number of infectious diseases. Microbiology, immunology, physiology, biochemistry and other medical specialties were developing rapidly. Insects had recently been incriminated as the vectors of certain diseases, including malaria. Medical

research was expanding, and some progress had been made in applying the new discoveries to the prevention of disease. However, the health situation in the United States still left much to be desired. Most of the endemic diseases were still prevalent, and at times they caused serious epidemics. The troops in the Spanish American War were seriously crippled by typhoid and the disease death rates were seven times as high as those caused by battle injuries. In spite of quarantine, the country was still being invaded by exotic diseases. The death rate for the year 1900 was 17.2 per thousand, the infant mortality was more than 100 per thousand, and the life expectancy was only 47 years.

From this time on, the picture became brighter and much progress has been made. Although it is a temptation to trace the course of that progress, it will serve our present purpose merely to show that a measurable improvement has been made and to indicate some of the factors concerned.

A careful study of these factors reemphasizes the importance of fundamental medical research to the improvement of health. It also shows that unless there is intelligent planning and vigorous application of the knowledge available, considerable time may be required to translate the products of research into action. This lag shows up in the vital records of the first two decades of the present century—a period when there was little popular or professional interest in public health, when trained health workers were scarce, and when the administration of official health services was left largely in the hands of incompetent politicians. Since that time, interest in preventive medicine has been increasing. Under the stimulus of various voluntary health agencies and philanthropic foundations, special schools have been established for the training of public health administrators; governmental health agencies have become more active at community, state and federal levels; and the total health coverage of the nation has been gradually expanded. The greater interest of the people and of the Federal Government during the last two decades is indicated by such significant events as President Hoover's White House conference on child welfare in 1930, and President Roosevelt's program of national security in 1935 which resulted in the Social Security Act. This legislation provided better national health services under the leadership of the United States Public Health Service and, at the same time, it has insured considerable independence of action by the states and their communities. When our country entered World War II, this program was well under way, and American health had reached a relatively high level. At that time the crude death rate for the Registration Area had decreased to a low of about 10.8 per thousand, the infant mortality had dropped to 47 per thousand live births, and the average life expectancy at birth had risen to about 64 years.

The unusual hazards of the war afforded a crucial test of our health resources. The success with which this test was met is known to all of us. The enormous war-time health program was actively supported and operated

by the united professions of medicine and public health, both civilian and military, although it was spearheaded by the programs of the Army and Navy. In the Army alone, more than 10 million men were mobilized to serve in some of the most unhealthful regions of the world; yet the disease rates were lower than in any of our former wars. Military medicine and surgery reached a high degree of efficiency. Many of the diseases which crippled our troops in previous wars, such as smallpox, typhoid, typhus and tetanus, were completely controlled. Other infections, especially malaria and the dysenteries, caused considerable disability in overseas theatres. However, there were no great epidemics, and the disease death rate was only 0.6 per thousand. This is a relatively low figure when compared with the rate of 15.6 for the first world war, and with 25 for the Spanish American war.

In commenting on this record, Winslow, Boudreau and Hume (1947) recently made the following statement: "Our allied armies planned their defenses against disease as carefully and scientifically as they planned for protection against airplanes and submarines; and it is an astounding fact that World War II was the first major conflict in history which was not followed by major epidemic diseases. Public health science has at its disposal today defensive weapons of unparalleled power and effectiveness."

Civilian health also continued to improve. Last year (1947) the death rate for the entire nation reached a new low of 10 per 1,000, and the expectation of life at birth rose to an all-time high of about 66 years.

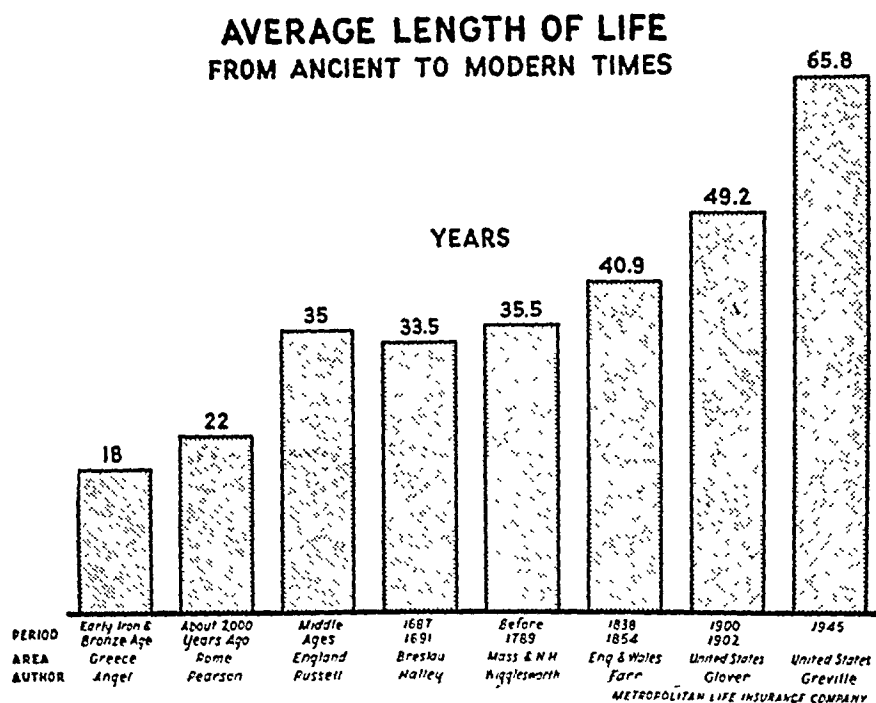


FIG. 1.



## UNSOLVED PROBLEMS

This is an excellent record of progress, especially when viewed against the background of the profound medical ignorance of the recent past. However, when one compares the death rates for different diseases in 1900 with the rates in recent years, it is apparent that the improvement has not been general. As shown in figure 2, the most spectacular reduction in mortality has occurred in the diseases that commonly attack children and young adults, but there has been little improvement in the rates for the degenerative conditions which afflict people in the later half of life. The main reason for presenting this graph, however, is to emphasize the fact that many people still die of diseases which are preventable, such as the infections included in the venereal, intestinal and insect-borne groups.

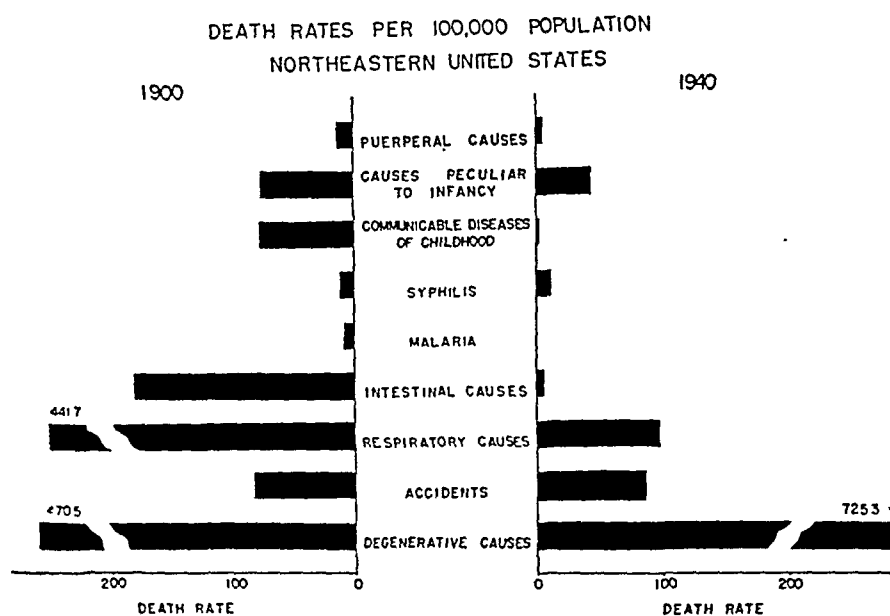


FIG. 2.

If one goes further and considers the sickness and disability caused by disease, additional health problems become apparent. We do not have the morbidity or disability rates for the entire country since 1900; however, most of the important diseases are now reportable, and the prevalence of certain groups of these diseases in 1946 is indicated in figure 3. This graph brings out the fact that a reduction in mortality alone is not enough to warrant the conclusion that any disease is under control. It deserves closer study by those who speak loosely of the conquest of infectious disease as a job that is finished.

One can visualize the unfinished task by considering briefly the present status of some of the more important groups of diseases and conditions included in these graphs.

1. *The Problems of Maternity and Infancy.* It is suggested that we start with the problems of maternity and infancy. Maternal mortality has

been decreased enormously within the last decade by improvements in the practice of obstetrics; and the maternal death rate, which was about 6 in 1937, reached an estimated low of 1.3 last year. The infant mortality has also declined from well over 100 per thousand in 1900 to an estimated 34.0 in 1947—a reduction of about 66 per cent. Earlier, this reduction was gradual, and apparently it resulted from various factors, including: the general improvement in living conditions, better sanitation, safer milk supplies, and better medical practice. During the last decade, the mortality has decreased more rapidly through the development of special pediatric care and child health services. The improvement, however, has not been uniform. In 1944, for example, when the total infant mortality for the United States was about 40.0, some of the states still had rates of 68.0, or more, indicating that serious health problems still exist in this field. The national survey

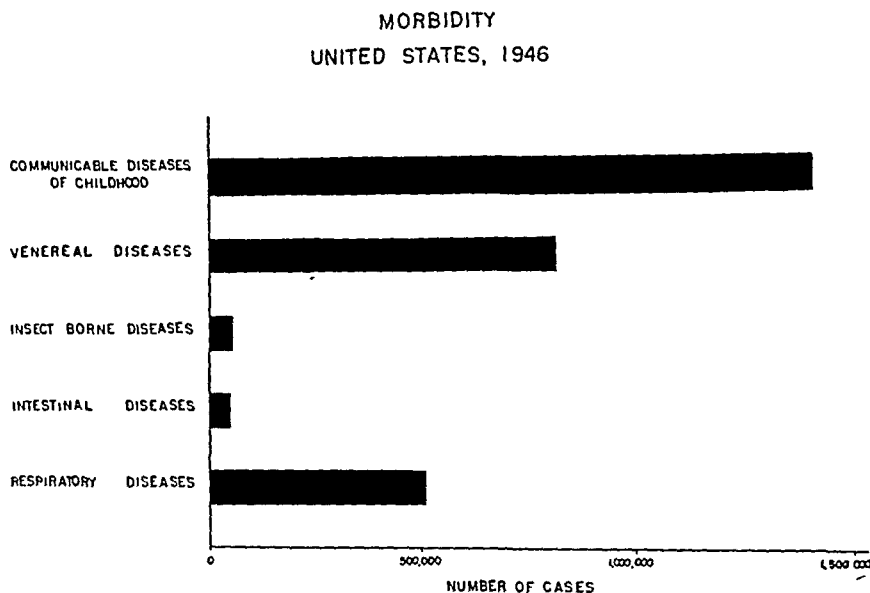


FIG. 3.

of child health services now being made by the Academy of Pediatrics, should help to define these problems and point the way to further improvement.

2. *Diseases of Childhood.* An even more remarkable reduction has occurred in the death rates for the communicable diseases of childhood. Fifty years ago, the combined mortality rate for measles, scarlet fever, whooping cough, diphtheria and meningitis was 75 per 100,000. In 1940, it was only 2.5—a reduction of about 97 per cent. However, this group of infections illustrates the fact that death rates may be reduced without a corresponding decrease in morbidity. In 1946, for example, measles ranked first among all the communicable diseases reported in the United States—with a total of about two-thirds of a million cases. Moreover, five of the ten leading communicable diseases reported that year were childhood infections. Chickenpox caused a quarter of a million cases, mumps 160,000, scarlet fever

118,000, and whooping cough 104,000. Yet none of these infections appeared among the 15 major causes of death in 1945, the latest figures available, although whooping cough is still an important cause of mortality in early life.

The decreased mortality for these diseases cannot be attributed to specific prophylactic measures. It has resulted largely from the use of more effective chemotherapeutic agents and to a general improvement in treatment and medical care. The fact that they are still leading causes of sickness, and that they produce much suffering and disability, makes it important to continue the search for methods with which to prevent them.

Epidemic meningitis is less important as a cause of death, since effective methods are available for treatment with the sulfonamides. Army field investigations show that sulfadiazine may be used effectively for the cure of meningitis carriers and for controlling epidemics, but better methods are still needed to prevent this disease.

Diphtheria belongs in a different category, for it is a preventable disease. The death rate has shown a larger decline than any of the other childhood infections. Before 1921, this resulted from the fact that more was known about its diagnosis, epidemiology and control; and antitoxin was available for specific treatment. Since that time both the mortality and morbidity have been decreased enormously by the immunization of large groups of children. Many of these immunization programs were stopped during the war, and diphtheria has increased slightly in the last two years. In 1946, for example, there were more than 16,000 cases and 1,300 deaths. These cases and deaths should not have occurred. The disease can be eradicated if all the states will provide for coördinated immunization programs to be conducted continuously in the schools, using diphtheria toxoid.

Poliomyelitis also presents a different problem, since there is no information as to specific treatment or prevention. In 1946, 25,000 cases were reported in the United States. Better methods for medical care and rehabilitation have been developed and it is hoped that the researches sponsored by the National Foundation for Infantile Paralysis and other agencies may eventually lead to its control.

3. *Respiratory Diseases.* The acute respiratory diseases, including the common cold, influenza, and the pneumonias, also present serious problems in prevention. In the records for 1945 and 1946 pneumonia and influenza were still listed among the 10 leading causes of disease, and also the 10 leading causes of death. However, the death rates are decreasing rapidly and they will be reduced further by the more general use of the sulfonamides and penicillin.

Progress is also being made in the development of immunizing agents. Researches sponsored by the Army Epidemiological Board show that several types of pneumococcus pneumonia can be prevented by immunization with polysaccharide antigens (Blake, 1945). The extensive use among troops of the Army influenza vaccine, developed by Francis and his co-workers of

the Influenza Commission, shows that protection is afforded against certain types of virus, and suggests the possibility of controlling this disease with vaccines containing a wider range of viruses.

The common cold is an important cause of temporary disability and economic loss. It has been estimated that colds cause the people of the United States to suffer discomfort and reduced efficiency for about one and one-half billion days each year. The annual cost has been estimated at more than 420 million dollars in lost wages plus sufficient expense for drugs and medical care to make a total of about one billion dollars. Thus the common cold still remains a major challenge to preventive medicine.

Pulmonary tuberculosis has shown a progressive decline in morbidity and mortality for more than a quarter of a century. Since 1921 the death rate has decreased from about 100 per 100,000 population to around 35 in 1946. The task of control, however, is still a difficult one. There are now at least half a million active cases in the population. In 1946 about 118,000 new cases were reported, and there were about 50,000 deaths from all types of tuberculosis. The campaign to eliminate this disease must be continued, using the newer methods for detection treatment and rehabilitation. BCG vaccine is being used on a limited scale and conservative opinion indicates that this procedure should probably be restricted to persons who are unusually exposed to the infection.

4. *Intestinal Infections.* The enteric diseases can all be prevented. Typhoid and the paratyphoid fevers can be controlled by vaccination. Except for veterans, however, the civil population has not been extensively immunized. Therefore, the civilian control of typhoid fever and of the other intestinal infections has been brought about largely through environmental sanitation, including improvements in the disposal of sewage and in the protection of water, milk and food. The reduction in typhoid has been most spectacular. In 1945 only 5,000 cases were reported in the United States, and during 1946, 41 American cities reported that there had not been a single death from typhoid fever in their populations during the previous two years.

The record of the other intestinal diseases is less satisfactory. Reports for 1945 show that the dysenteries, diarrhea and enteritis caused about 55,000 infections and more than 11,000 deaths. The continued appearance of these filth-borne infections is a national disgrace and calls for preventive action.

5. *Insect-borne Diseases.* The insect-borne diseases are also preventable, but they are by no means controlled. Malaria continues as a common cause of disability and chronic illness throughout the South, and the 61,000 cases reported in 1945 probably represent only a small proportion of the total infections. The gigantic wartime mosquito control program carried on by the armed services and the civilian public health agencies kept the army incidence rates for malaria contracted in this country at extremely low levels and caused an enormous decrease in civilian infections. This program should be continued.

In 1944 about 5,000 cases of murine typhus were reported, but the total incidence is believed to be much higher. Dengue fever is endemic in the South, and on occasions it causes extensive epidemics. Sylvatic plague exists among rodents over a wide area of the western states, and since no one can predict when it might become epidemic in man, it constitutes a potential menace. Plague vaccines are available, but the degree of protection which they afford is not known. Recent reports indicate that sulfadiazine, and possibly streptomycin, may be used effectively for treatment. This smoldering hazard should be removed.

Other important insect-borne diseases now endemic in the country include: Rocky mountain spotted fever, tularemia, and various types of virus encephalitis. The attack on these diseases should be directed toward the insect vectors and, when applicable, against rodent reservoirs of infection.

7. *Venereal Diseases.* The venereal diseases can also be prevented, but they continue to be a major health problem. In 1946 gonorrhea was the second of the 10 leading causes of disease, with more than a third of a million reported cases, and syphilis was third, with practically the same number of reported infections. In 1945 syphilis killed 14,000 people and was twelfth among the causes of death. The new methods of treatment with penicillin provide valuable weapons with which to intensify the attack on these diseases. The methods of prevention are known and these diseases should be controlled.

8. *The Chronic Degenerative Diseases.* Because of the increasing age of the population, the chronic degenerative diseases now rank as the most important causes of death, and are responsible for an enormous amount of sickness and disability. Last year the leading causes of mortality were: heart disease, cancer, cerebral hemorrhage and nephritis. According to Boas (1947) the most prevalent are rheumatism, heart diseases, arteriosclerosis and hypertension, and hay fever and asthma; while the most disabling are: nervous and mental diseases, rheumatism, heart diseases, and arteriosclerosis and hypertension.

Failure to control these diseases reflects the general ignorance concerning their underlying causes; and emphasizes the need for basic research aimed at the discovery of better methods of prevention, treatment and rehabilitation.

Such preventive services as are now available must be applied by the physician to the individual. They include early diagnosis of incipient disease through periodic physical examinations followed by correction of any defects found, and advice as to how to maintain normal health. This requires initiative on the part of the patient, a personal relationship between patient and physician, and adoption of the preventive viewpoint by the latter. Responsibility for the prevention of death from cancer, diabetes and other conditions in this group rests primarily with the medical practitioner and will continue to do so until better prophylactic methods can be found.

Official health agencies are also concerned with these problems and are becoming increasingly active in promoting adult health through education of

the public, and the initiation or provision of the diagnostic and other facilities required for better treatment and rehabilitation. At present health departments are actively engaged in such important fields as cancer control, industrial hygiene and mental hygiene.

9. *Smallpox*. A review of our remaining health problems would not be complete without mentioning smallpox. I have saved smallpox until last because it affords a spectacular example of the lag which still exists between the discovery of useful information and its practical application.

The value of vaccination has been recognized for a century and a half, but it has not been applied effectively in all parts of the United States. Consequently, the country is vulnerable to such invasions as occurred on the west coast in 1946, when the disease was imported from Japan and caused outbreaks in Washington and California; and again in 1947 when it was brought from Mexico into New York City. In both instances spread of the disease was stopped by extensive emergency vaccination programs. But this is an inefficient and costly way to control smallpox. In the New York episode the admission of a single case of smallpox into a modern hospital for contagious diseases was followed by the infection of at least 11 other persons, two deaths, a wave of popular hysteria that spread over the cities of the North Atlantic coast, and a mass vaccination program which involved at least 7 million people. This overtaxed the normal facilities for vaccine production and wasted millions of dollars. The whole affair could have been avoided if the unfortunate man who brought the infection from Mexico had been properly immunized before he left, or if his contacts in this country had all been protected by a satisfactory vaccination program.

This country's smallpox record is disgraceful. During the first quarter of the present century an average of over 40,000 cases was reported annually, and it was not until 1942 that the total fell below 1,000 cases per year. Even in 1945 and 1946 the annual totals were about 400 cases. Last year smallpox occurred in practically every country in the world and in many cases it reached epidemic proportions. At present, quarantine officers are alerted to prevent introduction of the disease from abroad. This would be unnecessary if our whole population was immune. If this country's experience with the prevention of smallpox affords an index of the efficiency with which all its other preventive measures are being practiced, there is ample room for improvement.

With the right sort of health education and the development of sound vaccination regulations, the continuing menace of smallpox can be eliminated in this country. In fact the disease could be controlled throughout the world within a relatively short period of time. An example of what can be done is afforded by the recent vaccination of the entire Japanese nation—a total of 78 million people—as a part of the comprehensive health program inaugurated and directed among the civilians of Japan by the United States Army.

In this brief review, I have mentioned only a few of the health problems with which we are faced today. We can all think of others—such as those

posed by occupational and industrial hazards, the high accident rates, nutritional deficiencies, the housing shortage, the need for rehabilitation, the pollution of our rivers with sewage and industrial wastes, and the need to protect our national water supplies.

Moreover, if one is to be realistic, it must be assumed that new problems may appear without warning next year or next week. For example, pandemic influenza will undoubtedly return some day, and plans should be made to meet it. Also, the country will probably be invaded again by yellow fever from Africa or South America, or by cholera or virulent plague from India or China, or by other exotic diseases from other countries, and we must be prepared to recognize such diseases and prevent their spread. Finally, we may be confronted some day with the still unknown hazards of atomic or biological warfare waged—not in some far-off land, but—in the streets of San Francisco, Chicago, New York and Washington.

### CONCLUSION

Now that we have defined preventive medicine broadly as the sum total of all those activities required to prevent disease and to keep well people well, have indicated its past contribution to the nation's health, and have pointed out some of the numerous health problems that remain unsolved, it is time to consider what can be done to meet the present challenge.

I have no intention of trying to tell this audience how to organize a national program of health. We all know that there is an important job to be done which will require the coördinated application of the best services available in both curative and preventive medicine. We also know from experience during the recent war what great potentialities for unselfish, united service exist among the scientists who make up the professions of medicine and public health, and I am sure we all have faith in their ability to meet this challenge.

It is obvious that immediate action should be taken to apply the knowledge now at hand to the eradication of preventable sickness, to the elimination of unnecessary death and disability, and to the rehabilitation of the physically and mentally unfit. It is equally apparent that adequate community health services and first class medical and surgical care should be made available to every man, woman and child in this country—not because of any idealistic concept that man has a parasitic right to demand health, but for the very practical reason that they are Americans, and their health is essential to the future strength and security of the nation.

It is also obvious that plans should be made for the future improvement of these services through better education and more research. The instruction in our medical and dental schools should be improved and geared up to Osler's vision of preventive medicine as the medicine of the future. Better and more adequate training should be provided in our schools of public health, and the principles of health should be taught to all Americans. Basic

medical research should be intensified and amply supported in order to develop better methods with which to control disease and promote health. It seems ridiculous that political considerations have held up the establishment of the long-delayed National Research Foundation. But you are familiar with these things, and it is not necessary to discuss them further. Before closing, however, I do wish to emphasize the fact that what we really need in order to meet the challenge of the future, is united, objective leadership within the ranks of medicine and public health.

With such leadership, the task should not be too difficult, for the people of this country sincerely want health. The experience of the recent war impressed them with the importance of preventive medicine. Strong tides of popular interest in public health are now running through this country and the people are ready to take whatever steps may be required to release themselves and their children from the unnecessary burden of preventable sickness and death. This rising tide of interest is reflected in the confusing deluge of bills which have recently been presented to the Congress in the hope of providing a more effective national health program. The unsatisfactory nature of many of these bills is indicated by the violent disagreements they have aroused within the ranks of the professions of medicine and public health. Such controversies must be even more confusing to the layman than they are to many of us. He must wonder why his medical leaders do not sit down together and draw up the blueprint for a sound and realistic health program which they can agree upon, and which is suitable for operation in our democratic society of free men. I am sure we all agree that the man in the street and the lawmaker do have a right to expect this sort of united leadership.

There is no question that the great body of unselfish men and women included in the professions of medicine and public health are vitally interested in making better health available to the people; also, that they alone are qualified to make sound plans by which to accomplish this. However, from the present chaotic status of health legislation, it is obvious that we are split into opposing groups that have not been able to agree—a situation that must remind the layman of current world politics or of Nero's fiddling in ancient Rome. This disturbing spectacle is decreasing the prestige of our professions, and, unless corrected, our lawmakers may be expected to adopt the attitude that if the leaders who have the primary responsibility for health cannot get together, they will seek leadership elsewhere.

It seems to me that a matter of such vital importance as the nation's health program should not be planned in a haphazard way, or by the hurried calling of emergency meetings of unrepresentative groups composed largely of laymen. I believe that health is sufficiently important to warrant calm, objective planning on a continuing basis by experts who represent the best available professional skill and judgment. I also believe that such experts should be able to agree on certain things that are needed and can be done



now, and that they should continue to seek a realistic solution for problems on which there is honest disagreement.

With this objective in mind, I wish to suggest that a permanent national advisory and planning council on health be organized with broad, official representation, including members elected from the American College of Physicians, the American College of Surgeons, the American Medical Association, the American Public Health Association, and all the other leading organizations competent to deal with medicine and public health. Such a representative council could concern itself with long-term planning for: (1) the improvement of teaching in medicine and public health; (2) the stimulation of medical research; and (3) the development of a sound program for the education of the public in the principles of health. In addition, this council could act in an advisory capacity to the government in all matters of health legislation.

In view of the fact that the American College of Physicians is composed of a large group of the elder statesmen in American medicine, it would seem appropriate for this distinguished organization to initiate the formation of such a council.

#### BIBLIOGRAPHY

- BLAKE, F. G.: Some recent advances in the control of infectious disease, *Rhode Island Med. Jr.*, 1945, xxviii, 409.
- EMERSON, H.: The unfinished job of essential public health service, *Am. Jr. Pub. Health*, 1948, xxxviii, i, 164.
- EMERSON, H.: Local health units for the nation, *Am. Jr. Pub. Health*, 1947, xxxvii.
- FISHBEIN, M.: A history of the American Medical Association, 1947, W. B. Saunders Co., Philadelphia, Pennsylvania.
- FRANCIS, T.: A consideration of vaccination against influenza, *Milbank Memorial Fund, Quarterly*, 1946, xxv, 5.
- GREGG, A. G.: Transition in medical education, *Jr. Assoc. Am. Med. Coll.*, 1947, iv, 22.
- LEAVELL, H. R.: The teaching of preventative medicine, *Jr. Assoc. Am. Med. Coll.*, 1947, iv, 210.
- PARRAN, T.: Surmounting obstacles to health progress, *Jr. Am. Pub. Health Assoc.*, xxxviii, 1, 168.
- PARRAN, T., and BOUDREAU, F. G.: The world health organization cornerstone of peace, *Am. Jr. Pub. Health*, xxxvi, 1, 267.
- Metropolitan Life Insurance Co., *Statistical Bulletin*, xxviii, 10, 2.
- REED, L. J.: Changing problems growing out of the change in composition of the population, *Jr. Am. Pub. Health Assoc.*, 1948, xxxviii, 160.
- RUSSELL, W. L.: The national mental health act, *Am. Jr. Psychiat.*, 1946, ciii, 417.
- SMILLIE, W. S.: Preventive medicine and public health, 1946, The Macmillan Co., New York.
- STIEGLITZ, E. J.: A future for preventive medicine, 1945, The Commonwealth Fund, New York.
- WINSLOW, C.-E. A.: Poverty and disease, *Jr. Am. Pub. Health Assoc.*, xxxviii, 173.
- WINSLOW, C.-E. A., BOUDREAU, F. G., and HUME, E. H.: Uniting the nations for health, Commission to Study the Organization of Peace, American Association for the United Nations, Inc., 1947, New York.

# PRELIMINARY REPORT ON THE BENEFICIAL EFFECT OF CHLOROMYCETIN IN THE TREATMENT OF TYPHOID FEVER\*

By THEODORE E. WOODWARD, M.D., JOSEPH E. SMADEL, M.D., HERBERT L. LEY, JR., M.D., *Baltimore, Maryland, and Washington, D. C.*,  
RICHARD GREEN, M.D., and D. S. MANKIKAR, M.D.,  
*Kuala Lumpur, Federation of Malaya*

A NEW antibiotic Chloromycetin has been clinically tested in the treatment of typhoid fever and has been found to exhibit significant chemotherapeutic effects. A description of the results in 10 cases is submitted as a preliminary report.

Chloromycetin is a crystalline substance obtained through processes of concentration and purification of cultures in liquid media of a Streptomyces sp. originally isolated by Burkholder,† and shown by him to possess anti-bacterial activity. Ehrlich and associates<sup>1</sup> in the Research Laboratories of Parke, Davis and Company carried out studies of the antibiotic activity of this Streptomyces which led to preparation of the crystalline antibiotic compound to which Ehrlich gave the name Chloromycetin.

Chloromycetin is a neutral compound containing both nitrogen and nonionic chlorine. In distilled water it withstands boiling for five hours, and in aqueous solutions over the pH range 2 to 9 is unaffected by standing at room temperature for more than 24 hours. Its solubility in water at 25° C. is about 2.5 mg./ml. and it is reported as very soluble in propylene glycol, methanol, ethanol, butanol and acetone. It is well absorbed from the gastrointestinal tract. Serum levels of the drug after oral administration have been found to be comparable to those obtained by parenteral injection. Present evidence indicates that the antibiotic is fairly rapidly excreted or inactivated.

Reported toxicity experiments on animals<sup>2</sup> indicate that when given intravenously in mice and intramuscularly in dogs Chloromycetin is well tolerated in single doses up to 100 mg. per kg. of body weight. Larger doses have been tolerated orally. On chronic parenteral administration in dogs the development of anemia has been noted. Variations in the white blood cells, and disturbance in hepatic or renal function have not been observed.

Initial studies of the antibiotic spectrum of Chloromycetin in vitro and in vivo in animals have been published.<sup>2,3</sup> These investigations have indicated outstanding effectiveness in rickettsial infections of chick embryos and mice. In addition Chloromycetin has been shown in vitro to be active against gram negative bacteria and *Borrelia recurrentis* and moderately active against *Mycobacterium tuberculosis* and gram positive bacteria.

Reports on the use of Chloromycetin in the treatment of human infections, up to the time of writing, have been confined to its use in epidemic typhus<sup>4,5</sup> and in

\* Received for publication May 16, 1948.

From The Department of Medicine, University of Maryland, School of Medicine; The Department of Virus and Rickettsial Diseases, Army Medical Department of Research and Graduate School; the Commission on Immunization of the Army Epidemiology Board; and from The Institute for Medical Research, Kuala Lumpur, Malaya.

† Dr. Paul R. Burkholder, Osborn Botanical Laboratory, Yale University.

scrub typhus.<sup>6</sup> In both of these rickettsial infections Chloromycetin has demonstrated marked therapeutic effectiveness.

In the course of an investigation of the chemotherapeutic value of Chloromycetin in the treatment of scrub typhus fever on the Malayan peninsula in the vicinity of Kuala Lumpur, the authors encountered numerous cases of typhoid fever which is endemic in this area, especially in the native population. Typhoid fever in this area tends to be of a clinically severe type, the febrile course not infrequently running to six or seven weeks.

Advantage was taken of this opportunity to test the efficacy of Chloromycetin in the treatment of this important type of enteric disease. The present report deals with the results obtained in 10 cases of typhoid treated with Chloromycetin. Chloromycetin used in this work was supplied by the Research Division of Parke, Davis and Company. Observations made on eight non-treated cases serve as a control.

The diagnosis in the 10 treated cases was confirmed by a blood culture positive for *Eberthella typhosa* prior to the initiation of specific therapy.

Chloromycetin was administered orally. The initial dose in each case was 50 mg./kilo of body weight. Thereafter 0.25 gm. was given every two hours until the temperature was normal and the same dose every three to four hours thereafter during the first five days of normal temperature. The total dosage per patient averaged 19.1 grams given over a period of 8.1 days. The drug was well tolerated and no clinical evidences of toxicity were observed.

The blood level for Chloromycetin was followed throughout the course of treatment. The blood concentration of the drug during the first 24 hours of therapy was of the order of 40 to 80 gamma per c.c. and during the subsequent three days remained at a level of 20 gamma per c.c. Workers at the research division of Parke, Davis and Company had previously shown that *E. typhosa* is inhibited by concentration of Chloromycetin of approximately one-quarter gamma per c.c. when the 50 per cent end-point technic is applied to fluid culture. Further details on blood concentrations and on the sensitivity of the typhoid organisms will be included in a later report.

*Course of the Disease in Treated Cases:* Cases in the first two weeks of their febrile course were selected for specific treatment. The majority of the 10 cases were started on the drug about the tenth day of their fever. The mean duration of known fever prior to treatment in the 10 cases was 9.5 days. The course of the disease after the start of Chloromycetin administration was followed by observations on the clinical condition, the duration of fever and the results of repeated blood, stool and urine cultures.

Evidence of improved general condition and lessened toxicity was usually apparent within 24 hours after the start of specific treatment, and increasingly thereafter. In the first seven cases the temperature reached permanent normal levels after three days of treatment. The mean in the 10 cases for



*Relapses:* Two of the 10 patients developed relapses with bacteremia occurring after afebrile periods of 10 and 16 days respectively. In both instances the recurrent infection responded promptly (three and two days) to a second course of Chloromycetin. It is of interest that the organisms isolated during the recurrence were as sensitive to Chloromycetin when tested in vitro as were those isolated initially.

*Complications:* Two serious complications, other than the recurrences noted above, were encountered among 10 patients. These consisted of intestinal perforation in one case, occurring on the second day of normal temperature; and, in a second case, massive intestinal hemorrhage developing in the fourth afebrile day. Following a more or less stormy course both recovered: one after supplementary therapy with streptomycin and penicillin and the other after transfusions of whole blood.

*Control cases:* The course of typhoid fever in the eight control cases is in striking contrast to that observed in the treated series. Of these eight cases, one died of the severity of the disease on the seventeenth day of his illness. The average total duration of fever in the remaining seven cases was 35 days.

The average treated case began treatment on the ninth day of his illness and thereafter had 3.5 days of fever while the average control case not receiving treatment on the ninth day ran fever for the ensuing 26 days.

### CONCLUSIONS

The antibiotic, Chloromycetin, exerts a specific therapeutic effect in patients with typhoid fever. The optimal schedule for administering the drug remains to be determined.

### BIBLIOGRAPHY

1. EHRLICH, J., BARTZ, Q. R., SMITH, R. M., JOSLYN, D. A., and BURKHOLDER, P. R.: Chloromycetin, a new antibiotic from a soil actinomycete, *Science*, 1947, cvi, 417.
2. SMITH, R. M., JOSLYN, D. A., GRUHZIT, O. M., McLEAN, I. W., JR., PENNER, M. A., and EHRLICH, J.: Chloromycetin: biological studies, *Jr. Bact.*, 1948, Iv, 425-447.
3. SMADEL, J. E., and JACKSON, E. B.: Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections, *Science*, 1947, cvi, 418.
4. SMADEL, J. E., LEÓN, H. E., LEY, H. L., JR., and VARELA, G.: Chloromycetin in the treatment of patients with typhus fever, *Proc. Soc. Exper. Biol. and Med.* In press.
5. PAYNE, E. H., KNAUDT, J. A., and PALACIOS, S.: Treatment of epidemic typhus with Chloromycetin, *Jr. Trop. Med. and Hyg.*, 1948, li, 68.
6. SMADEL, J. E., WOODWARD, T. E., LEY, H. L., JR., PHILIP, C. B., TRAUB, R., LEWTHWAITE, R., and SAVOOR, S. R.: Chloromycetin in the treatment of scrub-typhus. (Read before the International Congress for Tropical Disease, Washington, D. C., May 11, 1948.) *Science*. In press.

# CASE REPORTS

## THE TOXICITY OF BENADRYL: REPORT OF A CASE AND REVIEW OF THE LITERATURE\*

By BERNARD A. SACHS, Capt., M.C., A.U.S.,† *Baltimore, Maryland*

BENADRYL ‡ (b-dimethylaminoethyl benzhydriyl ether hydrochloride) is an anti-histaminic substance synthesized by Rieveschl and Huber and first reported by Loew, Kaiser and Moore.<sup>37</sup> Ever since the first clinical report by Curtis and Owens<sup>1</sup> toxic reactions have been mentioned frequently and prominently. A recent instance led us to review the literature and attempt to ascertain the frequency and character of toxic reactions and the relation of reaction to dosage. Toxic reactions have been variously termed side effects, side reactions, side actions, untoward reactions or untoward effects and these terms will be used interchangeably.

### CASE REPORT

The patient, a 28 year old white officer, first reported to a dispensary on October 24, 1946 with symptoms of prostatitis. He had an enlarged, tender prostate. On October 26 he received four 100,000 unit injections of penicillin one hour apart and sulfadiazine, one gram four times daily. The next day the sulfadiazine was discontinued because the patient developed a few mild urticarial lesions which soon became generalized. One day later the urticaria spontaneously disappeared. On November 1 he developed joint pains, swelling of the wrists and ankles and mild urticaria of the face and neck. This was treated with ephedrine capsules and frequent injections of epinephrine. Because the lesions progressively increased in severity and itched badly he was admitted to a station hospital on November 4, when he had marked urticaria of the face with large wheals over the neck, and periorbital edema closing his eyes. No other lesions were noted. The leukocyte count was 7600 with 61 per cent neutrophiles, 38 per cent lymphocytes and 1 per cent eosinophiles; hemoglobin was 15 grams and the urine, normal.

The patient was given 10 c.c. of 10 per cent calcium gluconate intravenously and 50 mg. of benadryl three times a day with some initial improvement. However, on November 11 one week after admission, the urticaria became more severe and involved the thorax and upper extremities. Furuncles were noted on his right forearm to which hot saline packs were applied; serous bullae soon developed in these areas. His temperature, which had previously been 100° or less, rose to 101.2° and pulse to 100. A penicillin skin test was read as four plus. The patient was given four grams of sulfadiazine because it was felt he had secondary infection of the lesions. The benadryl was continued. On November 12 the joint pains increased, the urticaria became very severe and some erythema multiforme-like lesions developed. He was then transferred to this hospital.

\* Received for publication April 21, 1947.

From the Regional Station Hospital, Fort Belvoir, Virginia.

† At present visiting Fellow in Medicine, The Johns Hopkins University School of Medicine.

‡ Diphenhydramine hydrochloride, New and Non-official Remedies, 1947.

On admission the patient complained of painful shoulder, elbow and interphalangeal joints bilaterally as well as "nervousness." One year before admission he had received penicillin for pneumonia but after two days this was discontinued and sulfonamide therapy initiated. He did not recall a skin eruption, drug fever, joint pains or urinary symptoms occurring at that time. He had no previous allergy. A maternal uncle had bronchial asthma.

His temperature was 101.2°, pulse 90 and respirations 24. (Blood pressure was not taken on admission because of edema but was subsequently 128 mm. Hg systolic and 64 mm. diastolic.) There were severe, massive, indurated wheals one to five centimeters in diameter with erythematous centers and irregular, elevated peripheries most numerous over the upper extremities and thorax, and confluent about the neck. Those on the dorsum of the hand had purplish centers. The patient had swelling and scaling of the face, especially the periorbital regions, and edema of the arms and hands with swelling of the interphalangeal joints bilaterally. Numerous confluent serous bullae were noted on the flexor surface of the right forearm. There were crepitant inspiratory râles over both lung bases posteriorly, a slight dry cough, and moderately tender axillary lymph nodes bilaterally.

The leukocyte count was 14,800 with 81 per cent neutrophils and 19 per cent lymphocytes. His urine and serologic test for syphilis were normal. Roentgen-ray of the chest showed a patchy density in the left base approximately three centimeters in length.

Soon after admission the patient was given 25 mg. (2.5 c.c.) of benadryl intravenously and 20 minutes later 10 mg. (1 c.c.) with no change in the pruritus, joint pains, skin lesions or periorbital edema. The only result noted was sudden drowsiness. That day he also received a total of 250 mg. of benadryl by mouth. The following day (November 13) the patient voluntarily stated he felt better and the itching had gone. However, the lesions objectively were of the same severity and had the classical appearance of urticaria with circinate and gyrate formations over the face, neck, shoulders, arms and back. Because of the dramatic results obtained in other patients,\*<sup>38</sup> an infusion of one gram of procaine in 1000 c.c. of 5 per cent glucose in distilled water was given over a period of three and three-quarters hours. Well circumscribed lesions were measured frequently before, during and after the infusion and no change was noted, subjectively or objectively. Since there was no improvement, beginning on the evening of November 13 the patient was given 100 mg. of benadryl every four hours. On November 14 some of the lesions on the thorax showed central clearing but the lesions on the back became more confluent. He also developed many wheals on his abdomen and a few lesions on his legs, but the edema of the hands decreased somewhat. By November 16 the joint pains had markedly decreased, the edema of the face had gone down considerably and the urticaria had completely disappeared from the back and legs. The patient continued to complain of "nervousness" as well as drowsiness and stated that for the past few days he had noticed subjective dizziness upon awakening and dryness of the mouth. Later this day (after having received 1500 mg. of benadryl in two and one-half days) the patient claimed mustard was being squirted on him from the walls and ceiling. He stated he smelled mustard and made other irrational statements. He telephoned the military police in reference to an allegedly stolen car and later asked the nurse to call the undertaker. During the day he appeared suspicious of all food and drink and when questioned replied that someone had been putting laxatives in them. His speech became jerky and rapid and a definite tremor of the extended hand was noted. At all times he was well oriented as to time, place and person. Because of these signs

\* One patient treated here had severe urticaria due to sensitivity to penicillin. This disappeared at once after an infusion of procaine. Some days later he had a recurrence of urticaria which responded very quickly to intravenous benadryl and did not return.

benadryl was discontinued on the evening of November 16 and he was given one gram of chloral hydrate as a sedative. The following morning the patient was quite rational and did not remember any of the previous day's unusual happenings. On November 17 the urticaria was completely gone. On November 18 a roentgenogram of the chest was clear. Subsequent blood studies revealed a leukocyte count of 7500 with 72 per cent neutrophils, 24 per cent lymphocytes and 4 per cent eosinophiles.

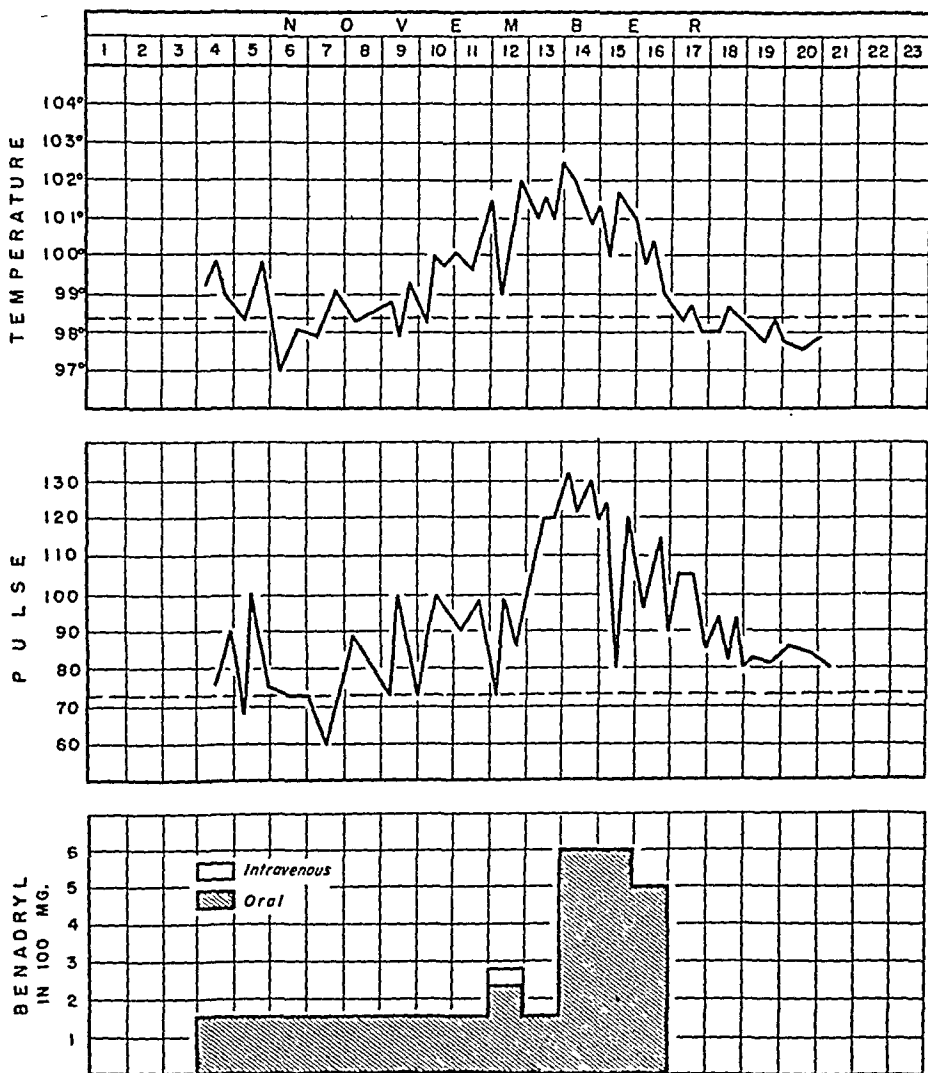


FIG. 1. Case report: temperature, pulse, benadryl dosage.

His course had been marked by an irregular temperature as high as 102.6° and tachycardia for the first five days (figure 1). He was asymptomatic after November 17. Before discharge on November 23 he stated that he recalled being "confused" on occasion during therapy. The relation of symptoms to benadryl dosage is illustrated by figure 2.

#### DISCUSSION

*A. Case.* A case is reported in which severe urticaria, edema and arthralgia resulted, probably due to either penicillin or sulfadiazine. It is felt that penicillin



D A Y	D A T E	SYMPTOMS AND SIGNS	MEDICATION RECEIVED	BENADRYL IN 100 MG.						TOXIC SYMPTOMS
				1	2	3	4	5	6	
1	Oct. 24	prostatitis								
2	25									
3	26		penicillin sulfadiazine							
4	27	mild urticaria								
5	28	urticaria gone								
6	29									
7	30									
8	31									
9	Nov. 1	urticaria, arthralgia, swollen joints	ephedrine epinephrine							
10	2		"							
11	3	urticaria increased, pruritus	"							
12	4	periorbital edema	barbiturates i.v. ca. gluc. oatmeal baths							
13	5									
14	6									
15	7									
16	8									
17	9		i.v. ca. gluc. epinephrine							
18	10	furuncles								
19	11	serous bullae	sulfadiazine							
20	12	severe urticaria, arthralgia, edema	i.v. procaine							nervousness drowsiness
21	13	urticaria increased								
22	14	urticaria more severe								dizziness dry mouth
23	15									
24	16	urticaria disappear- ing; edema, arthralgia gone	chloral hydrate							hallucinations tremor, jerky, rapid speech
25	17	urticaria gone								asymptomatic

FIG. 2. Case report: time-dose-symptom relationships.

was the cause of the sensitivity reaction for the following reasons: history of interruption of penicillin therapy during a previous hospitalization for pneumonia, four plus penicillin skin test, and the nature of the reaction. The patient was not relieved by ephedrine, epinephrine, calcium gluconate, intravenous benadryl or intravenous procaine. During eight days of oral benadryl at a dose of 150 mg. a day his lesions became progressively worse. The urticaria, edema and arthralgia cleared while benadryl was given at a dose of 600 mg. a day for two and one-half days. However, during this time he developed severe toxic reactions including dizziness, dryness of the mouth, visual and olfactory hallucinations, mental confusion, tremor, and jerky, rapid speech. It was necessary to discontinue the drug because of the severe reaction; the following morning the

patient was perfectly rational and normal. Hallucinations and jerky, rapid speech are reported for the first time.

*B. Frequency of Reactions.* Side reactions occurred in 46.4 per cent of 1210 patients.<sup>1-8, 10, 11, 13-18, 20</sup> In the 836 patients concerning whom adequate figures are given,<sup>1-4, 6-13, 15-17, 20</sup> drowsiness, found in 34.2 per cent, was the most frequently encountered toxic reaction. The soporific effect varies from a mild drowsy sensation to a deep slumber lasting 18 hours. Dizziness was the second most common reaction and was found in 14.1 per cent. Dryness of the oral cavity was found in 5.6 per cent, nausea in 2.6 per cent and nervousness in 2.3 per cent of the 836 patients. These are the most common reactions. Other reactions are noted in table 1. Asthma has been reported in 11 patients.<sup>4, 5, 7, 30</sup>

TABLE I

## Classification of Toxic Reactions Encountered with Benadryl\*

<p>I. Neuro-psychiatric</p> <p>Drowsiness<sup>1-19, 21-30, 40, 41</sup></p> <p>Dizziness<sup>1-5, 7-9, 11, 13, 16, 18, 19, 22-24, 26-28, 30</sup></p> <p>Nervousness<sup>2, 5-8, 16, 18, 23, 26, 27, 28, 30</sup></p> <p>Weakness<sup>1, 3, 5, 7, 11, 13</sup></p> <p>Fatigue<sup>2, 9, 13</sup></p> <p>Faintness<sup>3, 7, 8, 13, 25</sup></p> <p>Paresthesia<sup>4, 6, 11, 16, 40</sup></p> <p>Difficulty in coordination<sup>2, 16, 18, 30</sup></p> <p>Mental confusion<sup>5, 8, 18, 26, 39, 41</sup></p> <p>Headache<sup>16, 29, 40</sup></p> <p>Amnesia<sup>8, 9</sup></p> <p>Lassitude<sup>24, 27</sup></p> <p>Choking<sup>8, 10</sup></p> <p>Slurred speech<sup>39, 40</sup></p> <p>Malaise<sup>10, 42</sup></p> <p>Disoriented<sup>41, 42</sup></p> <p>Tinnitus<sup>2, 16</sup></p> <p>Stupor<sup>5</sup></p> <p>Narcolepsy<sup>5</sup></p> <p>Somnambulism<sup>5</sup></p> <p>Exhaustion<sup>5</sup></p> <p>Irritability<sup>5</sup></p> <p>Giddiness<sup>25</sup></p> <p>Slow speech<sup>40</sup></p> <p>Athetoid movements<sup>39</sup></p> <p>Acute melancholia<sup>40</sup></p> <p>Peripheral neuritis<sup>40</sup></p> <p>Insomnia<sup>7</sup></p> <p>Tremor<sup>8</sup></p> <p>Sense of relaxation<sup>2</sup></p> <p>Mental lethargy<sup>40</sup></p> <p>"Walking on air"<sup>16</sup></p> <p>"All gone feeling at pit of stomach"<sup>19</sup></p> <p>Acute hysterical reaction (i.v.)</p> <p>Apprehension (i.v.)</p> <p>Hallucinations (case report)</p> <p>Jerky rapid speech (case report)</p> <p>II. Alimentary</p> <p>Dry oral cavity<sup>2, 3, 5, 8, 12, 16, 18, 19, 22-27, 30</sup></p> <p>Nausea<sup>2, 4-8, 11, 12, 15, 29, 42</sup></p> <p>Vomiting<sup>4, 8, 11-13, 16, 17</sup></p> <p>Epigastric distress<sup>2, 20</sup></p> <p>Bad taste<sup>2, 5</sup></p>	<p>Diarrhea<sup>2, 13</sup></p> <p>Abdominal cramps<sup>7</sup></p> <p>Indigestion<sup>5</sup></p> <p>Heartburn<sup>42</sup></p> <p>Sore tongue<sup>5</sup></p> <p>Constipation<sup>2</sup></p> <p>Taste like chloroform (i.v.)</p> <p>III. Cardiovascular</p> <p>Orthostatic hypotension<sup>9, 19</sup></p> <p>Hypotension<sup>11</sup></p> <p>Palpitation<sup>5, 7, 42</sup></p> <p>Facial edema<sup>6, 40</sup></p> <p>Elevated pulse<sup>9</sup></p> <p>Excessive perspiration<sup>2</sup></p> <p>Cold extremities<sup>5</sup></p> <p>Vasospasm of fingers<sup>27</sup></p> <p>Pallor<sup>5</sup></p> <p>Collapse<sup>5</sup></p> <p>Shocklike reaction<sup>42</sup></p> <p>Hot flashes<sup>5</sup></p> <p>Bleeding tendency<sup>7, 2</sup></p> <p>Chills (i.v.)</p> <p>IV. Respiratory</p> <p>Asthma<sup>4, 5, 7, 30</sup></p> <p>Dry nose<sup>7</sup></p> <p>V. Genito-urinary frequency<sup>2, 11</sup></p> <p>Discomfort<sup>11</sup></p> <p>VI. Muscular, aching,<sup>1, 10, 11, 21</sup> twitching<sup>4, 39</sup></p> <p>Low back pain (i.v.)</p> <p>VII. Ocular</p> <p>Blurring of vision<sup>2, 5, 9, 19, 23, 30</sup></p> <p>Difficulty in ocular accommodation<sup>10, 12</sup></p> <p>Dilated pupils<sup>2, 9</sup></p> <p>Photophobia<sup>10</sup></p> <p>Dimmed vision<sup>42</sup></p> <p>VIII. Miscellaneous</p> <p>1. Generalized pruritus (i.v.)</p> <p>2. Aggravation of allergic symptoms<sup>5</sup></p>
---	--

\* Symptoms designated (i.v.) were seen only after intravenous administration.

Four of these had aggravation of existing asthma<sup>5</sup> and four had a previous idiosyncrasy to acetylsalicylic acid.<sup>7, 30</sup>

Toxic reactions appear to be more frequent when benadryl is given intravenously, occurring in 65 per cent of 43 patients<sup>2, 9, 15</sup> (table 2). Again drowsiness and dizziness are the prominent symptoms. The reactions encountered are, in general, more acute in onset, more severe, and of shorter duration. Weakness is seen much more frequently when the drug is given by vein. Six reactions ("acute hysterical reaction," chills, generalized pruritus, low back pain, taste like chloroform and apprehension) have been described only as a result of intravenous administration.

TABLE II  
Toxic Reactions with Intravenous Benadryl

	Author			Total	
	McElin and Horton <sup>2</sup>	McGavack, Elias and Boyd <sup>9</sup>	Lofstrom and Nurnberger <sup>15</sup>	Number	Per Cent
Dosage in mg.	10-120 in 10 min.	20-30	50-150		
No. of Pts.	26	10	7	43	100
No. of Pts. with Reactions	18	3	7	28	65
Reactions:					
Dizziness	12	1	4	17	39
Drowsiness	9	1	6	16	37
Weakness	0	1	6	7	16
Dry mouth	3	0	0	3	7
Tingling in legs	2	0	0	2	5
Chills or chilliness	1	1	0	2	5
Headache	0	2	0	2	5
Tinnitus	1	0	0	1	2
Low back pain	0	1	0	1	2
Pruritus	1	0	0	1	2
Taste like chloroform	1	0	0	1	2
Faintness	1	0	0	1	2
Hysterical reaction	1	0	0	1	2
Nervousness	1	0	0	1	2
Seasickness	0	1	0	1	2
Pallor	0	1	0	1	2
Sweating	0	1	0	1	2
Sl. decrease temperature	0	1	0	1	2
Vision hazy	0	0	1	1	2
Walking unsteady	0	0	1	1	2
Apprehension	0	0	1	1	2

Therapy was discontinued, at the will of the patient or physician, in 6.4 per cent of 1929 \* patients.<sup>1, 3-8, 11-13, 16-18, 28, 39, 40, 42</sup> If recovery from acute lesions was not so prompt this fraction would be greater.

*C. Character of Reactions.* Numerous untoward reactions have been described and may be roughly classified into eight groups: (1) neuro-psychiatric; (2) alimentary; (3) cardiovascular; (4) respiratory; (5) genito-urinary; (6)

\* The total number of patients in the series reviewed.

muscular; (7) ocular; and (8) miscellaneous (table 1). Toxicological studies in dogs reveal that high doses of benadryl cause ataxia, gastrointestinal reactions, nervousness and hyperesthesia of skin. Lethal doses in mice and rats (in which the oral LD50 is 167 and 545 mg. per kilogram respectively) produce violent excitement, convulsions and respiratory failure.<sup>32</sup> Intravenous injections in dogs produce hypotension of diphasic alterations in blood pressure depending upon the rapidity of injection.<sup>33</sup> Orthostatic hypotension and sustained hypotension have been observed in man.<sup>9, 11, 19, 40</sup> No alterations were noted in blood counts, blood chemistries and numerous other laboratory procedures repeated over long periods of time.<sup>2, 9</sup> No cumulative toxic reactions were noted in patients taking the drug for as long as seven months.<sup>1</sup>

Except perhaps for the occurrence of asthma after benadryl in patients sensitive to acetylsalicylic acid (each of these drugs contains a coal tar radical), the mechanism of toxic reactions has not been explained adequately.<sup>7, 30</sup>

*D. Relation of Symptoms to Dosage.* It may be stated only generally that untoward reactions are more common with higher doses. Profound reactions have occurred with a single 50 mg. dose, and 600 mg. has been given in one day without toxic effect.<sup>5, 13</sup> It appears, however, that the most severe toxic reactions occur most often with higher doses. Toxic reactions occur on some occasions and not on others with the same dosage in the same patient.<sup>5</sup> No correlation has been apparent between the occurrence of toxic reactions and either the nature of the disorder for which the drug was given or the character of the therapeutic result. There appears to be no correlation between the type of reaction encountered and the size of dose.

*E. Control of Toxic Reactions.* Side reactions can be made minimal in severity by reducing the dosage, giving the drug after meals, ordering the initial dose in the evening and prescribing stimulants such as black coffee, caffeine, ephedrine or amphetamine sulfate.<sup>4, 5, 12</sup> The last is the most effective stimulant.<sup>6, 11, 14</sup> If the untoward effect is mild the patient may continue at the initial dosage. A large number of patients develop tolerance and the untoward effect gradually disappears.<sup>7, 9, 16</sup> If the side reactions are severe, benadryl should be discontinued. The toxic effects disappear in from one to several hours after stopping the drug.<sup>1, 9, 18, 19 and present case report</sup> Only one case of prolonged toxic effect after cessation of therapy has been reported.<sup>40</sup> Addiction, in those who react with sleepiness, has not been encountered. Late side reactions, occurring for the first time after several months of therapy, have been reported by one author.<sup>18</sup> Benadryl should not be given in conjunction with sedatives or hypnotics because of the additive effect.<sup>12, 30</sup>

The patient must be warned about the possible toxic reactions since these may bring about other effects varying from mere embarrassment to severe injury.<sup>30</sup> These are usually due to the soporific side action. The drug may be a serious hazard when used by persons operating automobiles or machinery, or walking unescorted through traffic.<sup>4, 29, 30, 31</sup>

In evaluating the therapeutic use of benadryl fairly, one must consider the reactions discussed above. Although many of the reactions have been severe, the great majority have been mild. With one exception,<sup>40</sup> all of the reactions, regardless of severity, have been relieved shortly after discontinuing the drug or decreasing the amount given. This brief duration of reactions, associated

with the lack of cumulative drug effect greatly lessens the seriousness of benadryl toxicity.

### CONCLUSIONS

1. Toxic reactions from the therapeutic use of benadryl are common, occurring in 46.4 per cent of patients.

2. With intravenous therapy, toxic reactions are more frequent occurring in 65 per cent of patients, are more acute, somewhat more severe and of shorter duration.

3. The drug was discontinued because of toxic reactions in 6.4 per cent of 1929 patients.

4. Toxic reactions are unpredictable, occurring with small doses and occurring on some occasions and not on others at the same dosage in the same patient. In general, untoward reactions are more commonly encountered with high doses of the drug.

5. Toxic reactions, regardless of severity, are relieved shortly after discontinuing the drug. There is no evidence of cumulative toxic effect. Because of these two facts it must be concluded that the toxicity of benadryl, despite the frequency of side reactions, is low.

### SUMMARY

The chief limiting factors in the use of benadryl are the toxic reactions. A case of urticaria, edema and arthralgia probably due to penicillin sensitivity is reported. This patient did not respond to 150 mg. of benadryl a day but became completely well with a daily dose of 600 mg. On this high dosage the patient developed many untoward reactions including hallucinations and jerky, rapid speech which are reported for the first time.

The frequency of toxic reactions with oral and intravenous benadryl is cited. The five most common reactions are, in order of frequency, drowsiness, dizziness, dry oral cavity, nausea and nervousness. There are numerous variations in symptomatology. Some reactions have occurred only with intravenous use of the drug. The relation of symptoms to dosage is discussed. Mention is made of hazards that may result from toxic reactions. Measures for avoiding or minimizing untoward reactions are noted. The mechanism of these reactions remains obscure.

### BIBLIOGRAPHY

1. CURTIS, A. C., and OWENS, B. B.: B-dimethylaminoethyl benzhydryl ether HCl (benadryl) in treatment of urticaria, *Univ. Hosp. Bull., Ann Arbor*, 1945, xi, 25; *Arch. Dermat. and Syph.*, 1945, lii, 239.
2. McELIN, T. W., and HORTON, B. T.: Clinical observations on the use of benadryl: a new antihistaminic substance, *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 417.
3. O'LEARY, P. A., and FARBER, E. M.: Benadryl in the treatment of urticaria, *ibid.*, 1945, xx, 429.
4. WALDBOTT, G. L.: Clinical results with benadryl, *Jr. Allergy*, 1946, xvii, 142; *New antihistaminic drugs in allergic diseases*, *Jr. Mich. Med. Soc.*, 1946, xlv, 1051.
5. LEVIN, S. J.: B-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). Its use in allergic diseases, *Jr. Allergy*, 1946, xvii, 145.

6. KOELSCH, G. A., PRICKMAN, L. E., and CARRYER, H. M.: The symptomatic treatment of bronchial asthma and hay fever with b-dimethylaminoethyl benzhydriyl ether hydrochloride, *ibid.*, 1946, xvii, 151; *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 432.
7. EYERMAN, C. H.: Clinical experiences with a new antihistaminic drug, *Jr. Allergy*, 1946, xvii, 210.
8. JENKINS, D. E., SCHREIBER, E. O., and SHELDON, J. M.: Benadryl (b-dimethylaminoethyl benzhydriyl ether HCl) in the treatment of hay fever and asthma, *Univ. Hosp. Bull., Ann Arbor*, 1946, xii, 30.
9. MCGAVACK, T. H., ELIAS, H., and BOYD, L. J.: The influence of dimethylaminoethyl benzhydriyl ether HCl (benadryl) upon normal persons and upon those suffering from disturbances of the autonomic nervous system. Preliminary report, *Jr. Lab. and Clin. Med.*, 1946, xxxi, 560.
10. BAREFOOT, S. W., RILEY, K. A., and KUHN, B. H.: B-dimethylaminoethyl benzhydriyl ether HCl in the treatment of urticaria and related dermatoses, *N. Carolina Med. Jr.*, 1946, vii, 150.
11. BARNETT, S. E., BARBAS, F. M., and GOSS, S. B.: Benadryl in hay fever, asthma and vasomotor rhinitis, *Jr. Mich. Med. Soc.*, 1946, xlv, 771.
12. ZOLOV, B.: Benadryl—a new antihistamine agent in allergic disease, *Jr. Maine Med. Assoc.*, 1946, xxxvii, 126.
13. FRIEDLANDER, A. S.: The use of a histamine antagonist, b-dimethyl-aminoethyl benzhydriyl ether HCl in allergic disease, *Am. Jr. Med. Sci.*, 1946, ccxii, 185.
14. ARNOLD, H. L.: Symptomatic control of urticaria and its equivalents by "benadryl," *Proc. Clinic, Honolulu*, 1945, xi, 123; Benadryl in chronic urticaria, *Arch. Dermat. and Syph.*, 1946, liv, 71.
15. LOFSTROM, J. E., and NURNBERGER, E. E.: Irradiation sickness: histamine effect treated with benadryl, *Am. Jr. Roentgenol.*, 1946, lvi, 211.
16. SCHWARTZ, E., and LEVIN, L.: Benadryl in the symptomatic treatment of allergy, *N. Y. State Jr. Med.*, 1946, xlvii, 1233.
17. LOGAN, G. B.: The use of benadryl in treating some of the allergic diseases of childhood, *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 436.
18. O'LEARY, P. A., and FARBER, E. M.: Evaluation of benadryl in the treatment of urticaria, scleroderma and allied disturbances, *ibid.*, 1946, xxi, 295.
19. MCGAVACK, T. H., ELIAS, H., and BOYD, L. J.: Some pharmacological and clinical experiences with dimethylaminoethyl benzhydriyl ether HCl (benadryl), *Bull. N. Y. Acad. Med.*, 1946, xxii, 481.
20. NOTIER, V. A., and ROTH, G. M.: Treatment of hypersensitiveness to cold with benadryl: report of a case, *Proc. Staff Meet., Mayo Clin.*, 1946, xxi, 170.
21. TAUB, S. J.: The use of a new anti-histamine drug (benadryl) in allergic diseases, *Quart., Chicago Med. School*, 1945, vii, 6.
22. HARLEY, D.: Benadryl in hay fever, *Lancet*, 1946, ii, 158.
23. MACINNIS, H. F.: Clinical observations on the use of benadryl, a new anti-histamine compound, *Canad. Med. Assoc. Jr.*, 1946, lv, 476.
24. FRIEDLANDER, S.: Experimental and clinical evaluation of synthetic anti-histamine drugs, *Am. Jr. Med.*, 1946, i, 174.
25. KELLY, W. H.: Anti-histamine agents, *Jr. S. Carolina Med. Assoc.*, 1946, xlii, 209.
26. TODD, L. C.: Some clinical observations on the use of benadryl for the symptomatic relief of allergic conditions, *Ann. Allergy*, 1946, iv, 282; *N. Carolina Med. Jr.*, 1946, vii, 308; Urticaria—with observations on the use of the new anti-histamine drug, benadryl, *South. Med. and Surg.*, 1946, cviii, 1.
27. FRIEDLANDER, S., and FEINBERG, S. M.: Histamine antagonists: III. The effect of oral and local use of b-dimethylaminoethyl benzhydriyl ether hydrochloride on the whealing due to histamine, antigen-antibody reactions, and other whealing mechanisms; therapeutic results in allergic manifestations, *Jr. Allergy*, 1946, xvii, 129.

28. WILLIAMS, H. L.: Use of benadryl in the syndrome of physical allergy of the head: a preliminary report, *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 434.
29. BLANK, W. H.: Some clinical experiences with benadryl, *Jr. Med. Assoc. Alabama*, 1946, xv, 367.
30. BOWEN, R.: Benadryl, its therapeutic value in allergy, *Texas State Jr. Med.*, 1946, xlii, 188.
31. SLATER, B. J., and FRANCIS, N.: Benadryl, a contributing cause of an accident, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 212.
32. RIEVESCHL, G., JR., and GRUHZIT, O. M.: A toxicologic study of histamine antagonist b-dimethylaminoethyl benzhydryl ether HCl (benadryl), *Fed. Proc.*, 1945, iv, 150.
33. LOEW, E. R., MACMILLAN, R., and KAISER, M. E.: Anti-histamine properties of benadryl, b-dimethylaminoethyl benzhydryl ether hydrochloride, *Jr. Pharmacol. and Exper. Therap.*, 1946, lxxxvi, 229.
34. CODE, C. F.: A discussion of benadryl as an antihistaminic substance, *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 439.
35. FEINBERG, S. M.: Histamine and antihistaminic agents, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 702.
36. WELLS, J. A., MORRIS, H. C., BULL, H. B., and DRAGSTEDT, C. A.: Observations on the nature of the antagonism of histamine by b-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl), *Jr. Pharmacol. and Exper. Therap.*, 1945, lxxxv, 122.
37. LOEW, E. R., KAISER, M. E., and MOORE, V.: Synthetic benzhydryl alkamine ethers effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine, *Jr. Pharmacol. and Exper. Therap.*, 1945, lxxxiii, 120.
38. STATE, D., and WANGENSTEEN, O. H.: Procaine intravenously in the treatment of delayed serum sickness, *Jr. Am. Med. Assoc.*, 1946, cxxx, 990.
39. WEIL, H. R.: Unusual side effect from benadryl, *ibid.*, 1947, cxxxiii, 393.
40. SCHWARTZBERG, S., and WILLERSON, D.: Prolonged reaction to benadryl, *ibid.*, 1947, cxxxiii, 393.
41. BORMAN, M. C.: Danger with benadryl of self medication and large dosage, *ibid.*, 1947, cxxxiii, 394.
42. GEIGER, J., ROSENFELD, S. Z., and HARTMAN, D. L.: Unusual reaction following benadryl administration, *ibid.*, 1947, cxxxiii, 392.

---

## CHRONIC AURICULAR FLUTTER\*

By NATHAN M. FENICHEL, M.D., F.A.C.P., *Brooklyn, N. Y.*

DURING the past three years, three cases of auricular flutter in which the arrhythmia has persisted for prolonged periods have been seen. This is an occurrence at some variance with the general belief that auricular flutter is of short duration, a few weeks at most, and that its circus movement soon changes to either auricular fibrillation or else ceases with the resumption of normal sinus rhythm.

In the first patient, auricular flutter is still present after three years despite several attempts at interruption of the circus movement. In the second patient, the flutter remained for 15 months until his death from a cerebral hemorrhage. In the third patient the auricular flutter, after resisting all drug therapy, spontaneously changed to auricular fibrillation after several months.

\* Received for publication June 18, 1947.

From the Medical Divisions of the Jewish Hospital and the Kings County Hospital, Brooklyn, New York.

Occasional cases of permanent auricular flutter have been reported previously. As stated by White,<sup>1</sup> auricular flutter may be paroxysmal or permanent, usually lasting for hours or days, occasionally for weeks, but rarely for months or years. Sprague and White<sup>2</sup> in 1928 reported a case of auricular flutter of five years' duration. In their case the ventricular rate averaged 130 per minute, but at times it reached 260 per minute with release of the auricular-ventricular block. Lewis<sup>3</sup> in 1937 described a case of auricular flutter which lasted uninterruptedly for 24 years, and which maintained a ventricular rate of 140 per minute with 2 to 1 auricular-ventricular block. Kossman and Berger<sup>4</sup> in 1941 recorded a case of auricular flutter which endured 11 years. White<sup>5</sup> in 1944 mentioned an additional case of permanent auricular flutter of 15 years' duration.

## CASE REPORTS

*Case 1.* Mrs. M. Z., aged 38, was readmitted to the Medical Service of the Jewish Hospital on March 28, 1944 because of palpitation, epigastric distress, enlargement of the abdomen, and nausea due to sensitivity to digitalis. Physical examination disclosed cyanosis of the lips, orthopnea, moderate distention of the neck veins, and an irregular heart rate of 136 with a marked pulse deficit. The heart was found to be considerably enlarged both to the left and to the right. Systolic and diastolic murmurs were audible at the apex, and the pulmonic second sound was accentuated. There were some basal pulmonary râles, and the liver was tender and enlarged to 6 cm. below the costal margin. The diagnosis was moderate congestive heart failure, and rheumatic heart disease with mitral stenosis and insufficiency and possible tricuspid insufficiency.

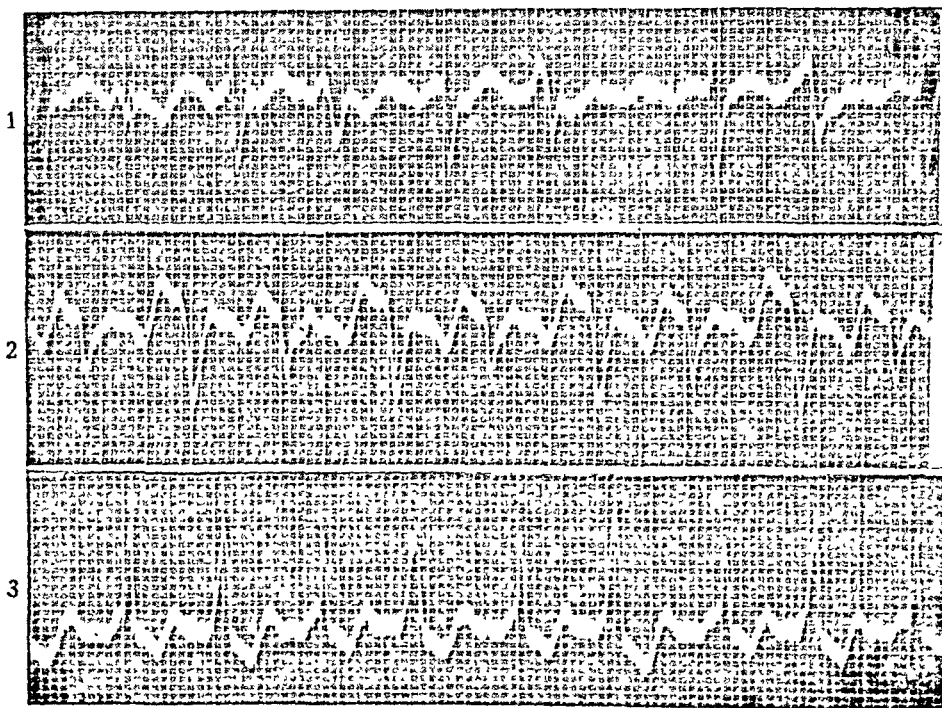


FIG. 1A. *Case 1*, April 3, 1944. Auricular flutter of 270 per min. The ventricular rate is about 130 and each alternate complex is a ventricular extrasystole producing bigeminal rhythm. The flutter waves are most conspicuous in Lead I where there is a temporary increase in the auriculoventricular block.



The arrhythmia was interpreted clinically as auricular fibrillation and additional digitalis was given on the day of admission. The following day distinct bigeminal rhythm was detected and the digitalis was withheld. On April 3, the electrocardiogram disclosed auricular flutter with a rate of 270, and a ventricular rate of 130 (figure 1A). Each second ventricular contraction was a ventricular extrasystole producing bigeminal rhythm in an otherwise 4 to 1 auricular-ventricular block. In Lead I, the flutter waves are clearly seen with a temporary increase in the block.

With only small doses of digitalis, the coupling disappeared within the next 10 days and the record of April 13 revealed auricular flutter of 240 with 4 to 1 block and a regular ventricular rate of 60. At this time rapid undulating pulsations of the cervical veins, due to the flutter, could easily be distinguished from the slow carotid pulsations.

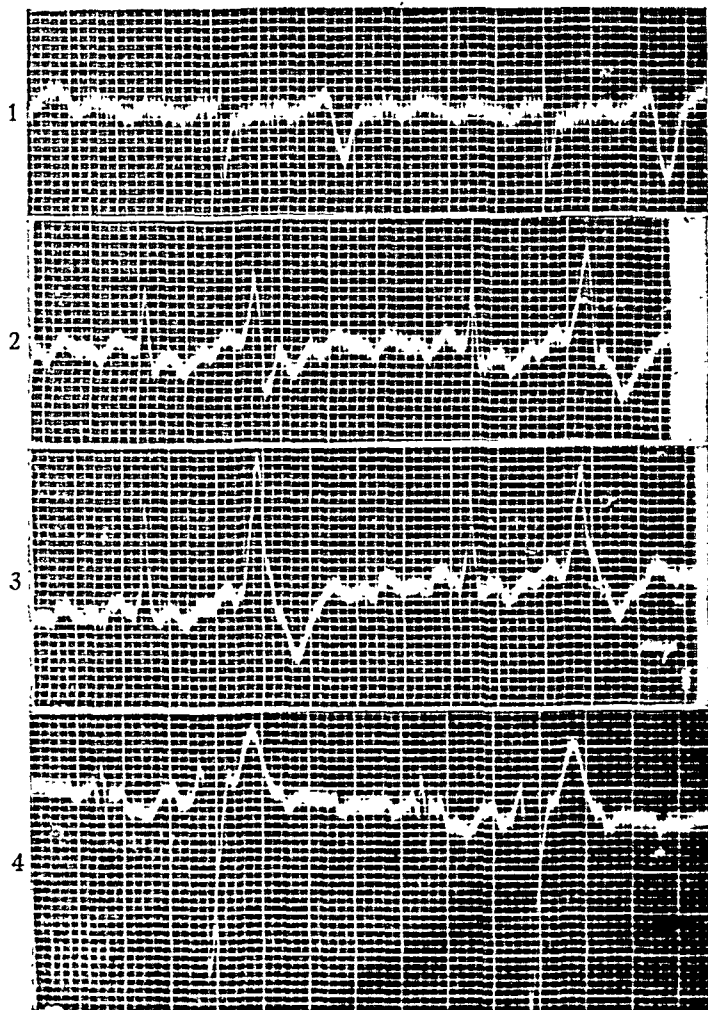


FIG. 1B. Case 1, July 27, 1944. Auricular flutter of 270. The ventricular rate is 90 and each alternate complex is a ventricular extrasystole producing bigeminal rhythm.

The patient maintained this status with half the usual maintenance dose of digitalis until her discharge, considerably improved, on May 3, 1944. She was given quinidine sulfate up to 0.8 gm. in eight hours, on several occasions, without altering the auricular circus movement. Larger doses of quinidine were not tolerated.

Since discharge from the hospital, she has been under observation for the past three years. She has been quite comfortable and able to perform light household duties. Her ventricular rate has been controlled with 0.1 mg. of digitoxin every two days, and she occasionally requires a mercurial diuretic. The auricular flutter, as confirmed by numerous electrocardiograms, persists and frequent episodes of bigeminal rhythm are also noted. Figure 1B taken July 27, 1944 shows auricular flutter with a rate of 270, and an average auriculoventricular block of 6 to 1. The normal ventricular rate is 45 and each of these complexes is followed by a ventricular extrasystole producing coupling. Figure 1C taken November 19, 1946 reveals an auricular flutter of 216 with 3 to 1 block and a regular ventricular rate of 72. The flutter waves are best seen in Leads I and IV. In Leads II and III, diphasic T-waves probably divide the flutter waves immediately following the QRS complexes.

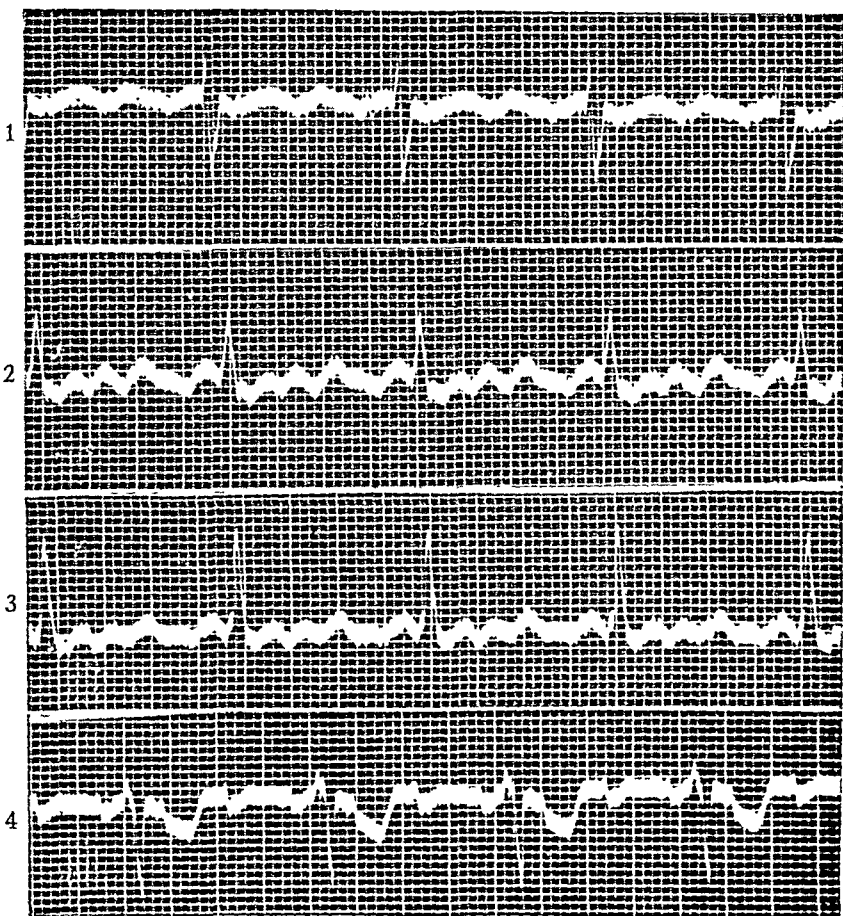


FIG. 1C. Case 1, Nov. 19, 1946. Auricular flutter of 216 with a constant 3 to 1 block and a ventricular rate of 72. The flutter waves immediately following the QRS complexes are split by diphasic T-waves in Leads II and III.

*Case 2.* Mr. B. W., aged 71, had been under observation since 1942 because of cerebral arteriosclerosis, moderate hypertension, and mild diabetes mellitus responding to a dietary regime. In June 1944 he experienced a sudden onset of precordial palpitation associated with a dry cough and increasing dyspnea. On examination on June 10 there was slight dyspnea and a few moist râles were heard at both bases. The heart rate was 145, regular except for an infrequent dropped beat. An electrocardio-

gram (figure 2A) disclosed auricular flutter with a rate of 290. The ventricular rate was about 145 with a predominant 2 to 1 auriculoventricular block and an occasional 3 to 1 ventricular response. The patient was digitalized within three days and quinidine sulfate 0.3 gm. t.i.d. was also prescribed. On June 16, the patient appeared much more comfortable and exhibited a regular heart rate of 75. However, on inspection in the supine position, the neck veins were seen to be undulating at an extremely rapid rate and persistence of the flutter was suspected. An electrocardiogram (figure 2B) now revealed an auricular flutter of 300 with a constant 4 to 1 auriculoventricular block.

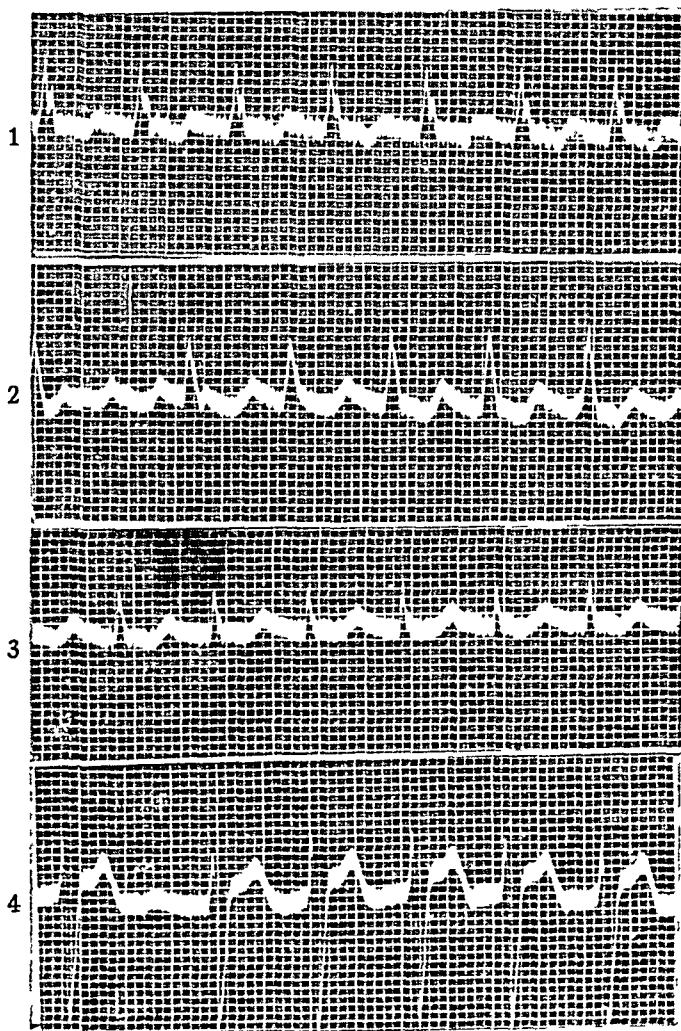


FIG. 2A. Case 2, June 10, 1944. Auricular flutter of 290 with a predominant 2 to 1 auriculoventricular block and a ventricular rate of about 145. The occasional 3 to 1 ventricular response is seen in Leads II and IV.

The patient was maintained on digitalis for the following 15 months, and on several occasions quinidine sulfate up to 2.0 gm. daily was administered without abolishing the auricular circus rhythm. He gradually developed congestive heart failure which responded to mercupurin injections. In May 1945, the electrocardiogram showed auricular flutter with a rate of 250, and an irregular ventricular rate of 80 due to a varying auriculoventricular block of 2 to 1, 3 to 1, and 4 to 1.

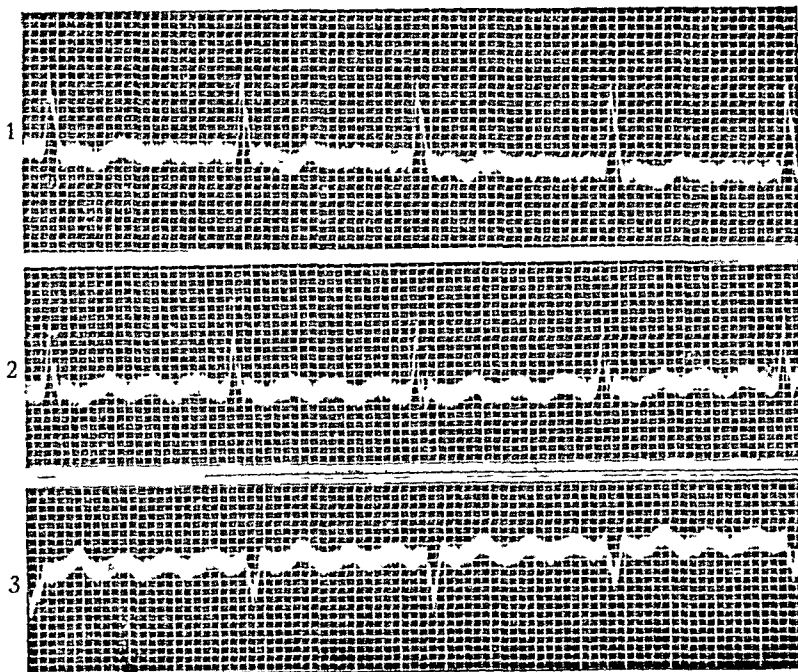


FIG. 2B. Case 2, June 16, 1944. Auricular flutter of 300 with a constant 4 to 1 auriculoventricular block.

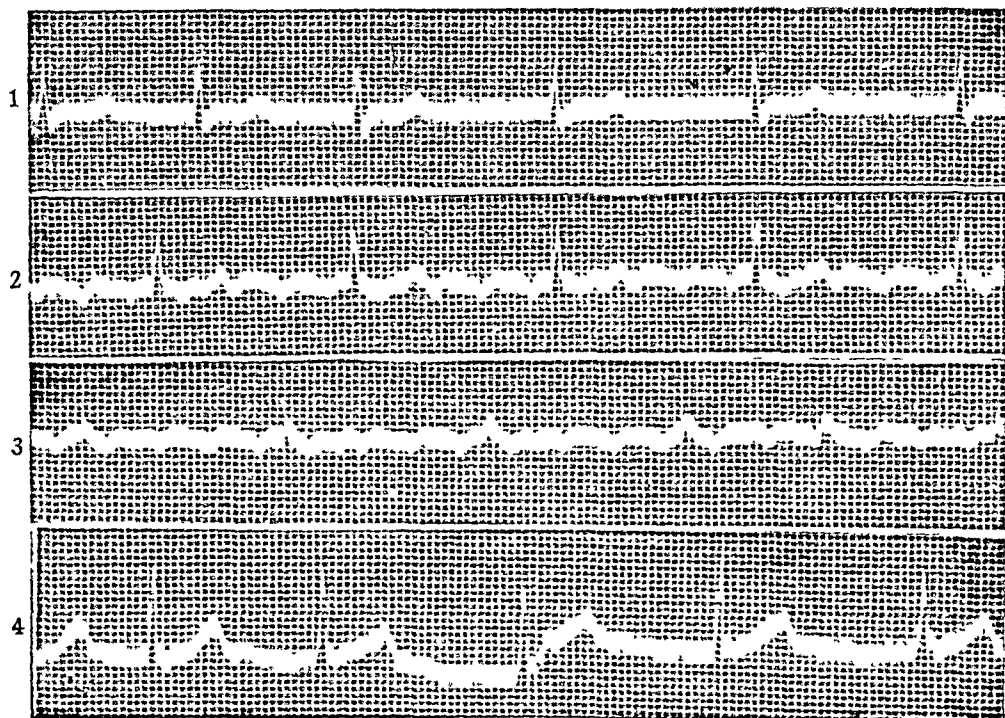


FIG. 3. Case 3, Aug. 10, 1946. Auricular flutter of 240 with a ventricular rate of 56. The auriculoventricular block varies from 3 to 1 to 5 to 1.

In September 1945 he lapsed into coma due to a cerebral hemorrhage and died within three days. The auricular flutter as revealed by the rapid pulsations of his cervical veins persisted until his death. Autopsy permission was denied.

*Case 3.* Mr. H. B., aged 77, was admitted to the medical service of the Kings County Hospital on August 9, 1946 because of pain and swelling of his right hand. He complained also of moderate palpitation experienced during the past few months. Examination disclosed an acute arthritis of the hand involving the wrist and interphalangeal joints. The cardiac rhythm was slightly irregular and the rate was about 60. His blood pressure was 210 mm. Hg systolic and 110 diastolic. Very rapid undulations of the cervical veins could be identified when the patient was lying flat in bed. The electrocardiogram of August 10 showed auricular flutter of 240 per minute with a ventricular rate of 56 and an auricular-ventricular block varying from 3 to 1 to 5 to 1 (figure 3).

In an endeavor to restore normal rhythm through the intermediate stage of auricular fibrillation, the patient was fully digitalized within three days. As observed in the daily electrocardiograms, the ventricular rate gradually decreased to 40 and the auriculoventricular block increased to as high as 9 to 1, but the flutter remained unaltered. Quinidine sulfate was then given in increasing doses up to 2.2 gm. within nine hours without any effect. However, on September 10, two days after the quinidine was discontinued and 10 days after all digitalis was withheld, the auricular rhythm spontaneously changed to fibrillation which persisted until his discharge, September 14. The arthritis of his hand gradually subsided with salicylate therapy.

As indicated by the history, the auricular flutter was probably present in this patient for several months prior to his admission and continued during one month of observation in the hospital.

#### COMMENT

Of these three patients with auricular flutter, the first patient suffered from rheumatic heart disease, and the other two from arteriosclerotic heart disease. Digitalis had no effect on the auricular arrhythmia in all three, but was required in the first two patients to increase the auriculoventricular block sufficiently to maintain a slow ventricular rate. The third patient exhibited a slow ventricular rate on admission, probably due to an organic block, and did not require maintenance doses of digitalis. Quinidine had no influence on the abnormal auricular rhythm of any of these patients.

Clinically in all three, the auricular flutter could be identified by rapid regular undulating pulsations of the cervical veins when the patient was supine and when the auriculoventricular block was greater than 2 to 1. With 2 to 1 block or less, the ventricular rate and hence the carotid pulsations were so rapid that their pulsations could not be differentiated from those of the veins.

The pulsations of the cervical veins in auricular flutter may sometimes be confused with unusually prominent a, c, and v jugular pulsations occurring with normal sinus rhythm when the venous pressure is high. In the latter instance, the pulsations are not regularly spaced and are of uneven amplitude throughout each cardiac cycle.

#### SUMMARY

1. Chronic auricular flutter is not as rare as is generally believed. Three patients are presented in whom the abnormal rhythm lasted over three years, 15 months, and several months, respectively.

2. Chronic auricular flutter may be treated just as chronic auricular fibrillation with a sufficient maintenance dose of digitalis to slow the ventricular rate adequately.

#### BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, 1944, The Macmillan Co., New York, p. 903.
2. SPRAGUE, H. B., and WHITE, P. D.: Auricular flutter. Report of a case of five years' duration with spontaneous restoration of normal rhythm, Jr. Am. Med. Assoc., 1928, xc, 1772.
3. LEWIS, T.: Auricular flutter continuing for 24 years, British Med. Jr., 1937, i, 1248.
4. KOSSMAN, C. E., and BERGER, A. R.: Auricular flutter of eleven years' duration with observations on esophageal electrocardiograms, Ann. Int. Med., 1941, xv, 128.
5. WHITE, P. D.: Heart disease, 1944, The Macmillan Co., New York, p. 906.

---

#### CODEINE ADDICTION \*

By CHARLES M. GRUBER, Ph.D., M.D., and GUY M. NELSON, M.D.,  
*Philadelphia, Pennsylvania*

For approximately 100 years codeine has been used in therapeutics with total disregard of its possible addicting properties. Since it has a feeble euphoric action the addiction liability is not great. The first case of true addiction to codeine was reported by Pelz<sup>1</sup> in 1905. The drug which had originally been given to this patient in 30 mg. ( $\frac{1}{2}$  grain) doses three times a day for "nervousness" was gradually increased to 1.5 gm. (22 $\frac{1}{2}$  grains) orally per day and ultimately to 3 gm. (45 grains). Treatment of this patient by the method of abrupt and complete withdrawal was followed by a definite abstinence syndrome, indicating a physical dependence upon codeine. In 1913, Sollier<sup>2</sup> reported a patient who took the drug regularly for the relief of rheumatic pains and whose tolerance had increased until within three years a daily dosage of 2 gm. (30 grains) was reached. In this case, as in the case described above, withdrawal of the drug caused typical abstinence symptoms.

Himmelsbach and his associates<sup>3</sup> have collected from the literature the reports of 99 codeine addicts. Of these, 74 were reported as presumptive and 25 as definite addicts. Many of the presumptive addicts would probably have been placed in the definite class had more of the history been given in the reports.

#### CASE REPORT

R. J. B., a white male, age 57, a physician, was admitted to Jefferson Hospital November 4, 1945, complaining of pain in the epigastrium which had persisted since 1937. His past history is relatively unimportant except that he had had the following known adult diseases and operations: Appendectomy, 1908; inguinal herniotomy, 1934; removal of left ureteral calculus, 1937; acute toxic hepatitis, 1937; chronic calculous cholecystitis, 1937; and cholecystectomy, 1938.

Physical examination showed an emaciated, well-developed male, in no apparent distress, but slightly lethargic. The breath had the odor of paraldehyde. Except

\* Received for publication April 5, 1947.

From the Departments of Pharmacology and Medicine, Jefferson Medical College, Philadelphia, Pennsylvania.

for some tenderness and rigidity in the epigastrium, a liver edge palpable 3 cm. below the costal margin, and scars due to former operations, the physical examination was negative.

Roentgen-ray studies of the chest and of the gastrointestinal system revealed no unusual finding. The electrocardiogram was essentially normal. The liver function (bromsulfalein) test was within the normal range. The urine was essentially normal except that a test for urobilinogen was positive in dilutions of 1 to 20; however, only one such study was made. The urea clearance was 89 per cent. The stool was normal in the amount of bile pigment content. Except for low red blood cell count, low hemoglobin content, and some basophilic stippling of the red blood cells, nothing unusual was noted in the blood. On admission, the red blood cell count was 3,400,000 per cu. mm. and the hemoglobin level was 68 per cent; just before the patient left the hospital these had become 5,000,000 per cu. mm. and 91 per cent, respectively.

On questioning, the patient admitted that he had taken paraldehyde and ten 20 mg. (1/3 grain) tablets of "Pantopon" before entering the hospital, because of pain he had suffered due to the long trip from one of the Southern states to Philadelphia. He insisted that only on occasion did he use either morphine or "Pantopon" for the relief of pain, but admitted that he did use codeine freely and on occasion whiskey to excess. He had taken 0.66 gm. (10 grains) of codeine per day for several months, but became tolerant to this dose, and during the past several weeks, previous to coming to the hospital, he had been taking, hypodermically, 4.8 gm. (72 grains) of codeine sulfate daily. The discovery of the true state of affairs came about in the following way. Since the fact that the patient was suffering from codeine addiction was not realized and since he had taken, just before entering the hospital, large doses of "Pantopon" and paraldehyde, the dose of codeine given the first day was relatively small (table 1).

TABLE I

Summary of Treatment Used and the Average Heart Rate of the Patient during the Withdrawal of Codeine

Days of treatment	Con- trol	1	2	3	4	5	6	7	8	9	10	11	12
Codeine sulfate in gm./24 hrs.	4.8	0.75	2.87	2.25	2.2	1.67	1.42	1.3	1.3	0.92	0.55	0.42	0.1
Demerol in mg./24 hrs.	0	0	0	400	500	600	500	600	500	500	500	500	0
Average heart rate	80	84	60	52	61	73	71	72	72	70	71	71	71

However, after the patient demanded 0.52 gm. (8 grains) of codeine one hour after having received 0.26 gm. (4 grains), the fact of his addiction was established; thereafter, the treatment for codeine addiction was relatively simple. In the following 24 hours he was given hypodermically 2.86 gm. (44 grains) of codeine sulfate in 0.26 gm. (4 grains) doses, as needed. This dose was gradually reduced until on the thirteenth day he received no codeine. Because of pain, of which he complained bitterly in the beginning of treatment, "Demerol" was started on the third day. This was given in 100 mg. doses hypodermically four to six times per day (table 1), and discontinued on the eleventh day. On the twelfth to the fifteenth days, inclusive, he was given hypodermic injections of sterile distilled water.

The withdrawal symptoms were marked and definite. He complained of increased pain in the abdomen, muscular weakness, leg cramps, and muscular twitching. He became restless, nervous, jittery, and was unable to sleep. Whether this was due

to the pain or due to the withdrawal of codeine cannot be stated conclusively; however, from the ninth day on, with a marked reduction in codeine intake, the patient slept well, complained of no pain, was talkative and stated that he felt fine. He continued to sleep well, remained pleasant and suffered no pain during the remainder of his stay in the hospital even though he received only acetylsalicylic acid, as needed, and injections of sterile distilled water. During the first three days of drug restriction the respiration rate decreased from 20 to as low as 12 per minute, the temperature dropped from 98.6° to 97.9° F., and the pulse rate from 80 to as low as 52 beats per minute with a corresponding insignificant fall in both systolic and diastolic blood pressures.

During the first eight days of treatment he lost 15 pounds in weight, which he slowly regained during his stay in the hospital. Several days after complete withdrawal of codeine he was informed of his addiction problem. While in the hospital he continued relatively symptom free; after leaving the hospital he went to his home, arranged his personal affairs, and then took his own life.

### SUMMARY

The above patient, we believe, had a case of true codeine addiction. Tolerance had been acquired over a period of years and, upon withdrawal of the drug, abstinence symptoms occurred similar to those noted after the withdrawal of morphine.

### BIBLIOGRAPHY

1. PELZ: Ein Beitrag zum Codeinesmus, *Med. Wchnschr.*, 1905, xxxi, 864.
2. SOLIER, P.: Un cas de codeinomanie pure, *Rev. de med. leg. et de jurisprudence med.*, 1913, xx, 359.
3. HIMMELSBACH, C. K.: Studies on codeine addiction, *U. S. Pub. Health Rep. Supplement*, 1940, No. 158, 2.



## EDITORIAL

### *Q FEVER*

IN 1935 the outbreak of an unknown fever among a large number of workers in a meat work in Brisbane, Australia, led Dr. E. H. Derrick, the Director of the Laboratory Section of the Queensland Health Department, to investigate the cause of the outbreak. These investigations, which lasted over several years, led to our first knowledge of what is now known as the clinical entity of "Q fever." In his first publication in 1937, Derrick<sup>1</sup> gave a thorough clinical description of nine typical cases of the infection and in addition reported his work on the nature of the virus causing the disease. He showed that guinea pigs are susceptible to Q fever; that they may be infected by inoculations of blood or urine from patients during the active stages of the disease and that after having recovered from their infection, the guinea pigs remained immune for many months to further inoculations. Guinea pigs killed during the active stage of their infection show on autopsy enlargement of the spleen and liver, and emulsions of both of these organs are highly infective to new guinea pigs. In the same year Burnet and Freeman<sup>2</sup> in Melbourne reported on further studies of the virus which had been isolated from Q fever patients by Derrick. They found that mice inoculated intraperitoneally with infected guinea pig liver showed enlargement of the spleen and liver with characteristic histological changes. In sections and smears of such infected mouse liver and spleen large numbers of rickettsial organisms were visible. These basic studies of Derrick and of Burnet and Freeman established the entity which is now widely known as Q fever.

In view of our more recent knowledge concerning the clinical course of Q fever, it is interesting to review the descriptions of the course of this disease given by Derrick, based on the nine patients included in his report. The onset of the illness in all cases was acute; first complaints were usually headache, pains in the back and limbs and fever. Four patients noted mild chilliness, two patients had a definite rigor. Fever in these cases was of very variable duration. In a milder type it lasted for approximately nine days. In other cases, however, the course was more prolonged, lasting from 14 to as much as 24 days. In only one of the nine patients was there a rash and this was of a not very specific character and did not appear until the fourteenth day of the illness. The white blood cell count was found within normal limits. In only two of these cases was cough mentioned as a symptom. However, in his discussion of the differential diagnosis of the disease, Derrick mentions that in some of the cases of Q fever, mild respiratory symptoms were present and that these patients were naturally regarded

<sup>1</sup> DERRICK, E. H.: "Q" fever, a new fever entity: clinical features, diagnosis, and laboratory investigation, *Med. Jr. Australia*, 1937, ii, 281-299.

<sup>2</sup> BURNET, F. M., and FREEMAN, M.: Experimental studies of the virus of "Q" fever, *Med. Jr. Australia*, 1937, ii, 299-305.

at first as suffering from influenza until the continuance of the fever excluded this diagnosis.

After the discovery of the rickettsial nature of the infection, Derrick, Burnet and Freeman suspected that because of the absence of rash and the failure to agglutinate any of the proteus strains, as well as on differential points in the morphology of the *Rickettsia* that had been demonstrated, it was probable that Q fever represented a new rickettsial disease which could not readily be classified in existing groups of rickettsial infections.

In 1938 Gordon E. Davis and Harold R. Cox<sup>3</sup> reported upon the recovery of a filter passing infectious agent from ticks of the species *Dermacentor andersoni* which had been collected near Nine Mile Creek, about 32 miles west of Missoula, Montana. Parker and Davis<sup>4</sup> demonstrated that this infectious agent could be transmitted to guinea pigs through the *Dermacentor andersoni* acting as a vector. Cox<sup>5</sup> in a later report in the same year described the infectious agent as a gram negative pleomorphic rickettsia-like organism, that occurred both intra- and extra-cellularly in the affected tissues of the guinea pigs.

In describing an infection in a laboratory worker who had been exposed to the virus derived from ticks, Dyer<sup>6</sup> was able to show that the serum of this individual had protective properties against infection in animals with the Q fever strain of rickettsia, and that in addition, guinea pigs infected with this patient's blood upon recovery were found immune likewise to the fever of the tick virus. He suggested the probability that these two rickettsial diseases were identical. Meanwhile, the name *Rickettsia burneti*<sup>7</sup> had been proposed for the agent causing the Australian infection, and the name *Rickettsia diaporica*<sup>8</sup> had been suggested for the causative organism in the American infection.

Exchange of infective material from these two infections between the National Institute of Health and the Walter and Eliza Hall Institute in Melbourne led to studies which conclusively proved that the two infective organisms were identical.<sup>9</sup> Because of the priority of Burnet's isolation of the rickettsia, the organism is now universally known as *Rickettsia burneti*.

<sup>3</sup> DAVIS, G. E., and COX, H.: A filter-passing infectious agent isolated from ticks. I. Isolation from *Dermacentor andersoni*, reaction in animals and filtration experiments, Pub. Health Rep., 1938, liii, 2259-2267.

<sup>4</sup> PARKER, R. R., and DAVIS, I. E.: A filter-passing infectious agent isolated from ticks. II. Transmission by *Dermacentor andersoni*, Pub. Health Rep., 1938, liii, 2267-2270.

<sup>5</sup> COX, H. R.: A filter-passing infectious agent isolated from ticks. III. Description of organism and cultivation experiments, Pub. Health Rep., 1938, liii, 2270-2276.

<sup>6</sup> DYER, R. E.: A filter-passing infectious agent isolated from ticks. IV. Human infection, Pub. Health Rep., 1938, liii, 2277-2284.

<sup>7</sup> DERRICK, E. H.: *Rickettsia burneti*: the cause of Q fever, Med. Jr. Australia, 1939, i, 14.

<sup>8</sup> COX, H. R.: Studies of a filter-passing infectious agent isolated from ticks. V. Further attempts to cultivate in cell-free media. Suggested classification, Pub. Health Rep., 1939, liv, 1822-1827.

<sup>9</sup> BURNETT, F. M., and FREEMAN, M.: A comparative study of Rickettsiae strains from an infection of ticks in Montana (United States of America) and from "Q" fever, Med. Jr. Australia, 1939, ii, 887-891.

Infections of laboratory personnel with the *Rickettsia burneti* have been a striking feature of the development of our knowledge concerning this organism. Such infections occurred in Derrick's Laboratory in Brisbane<sup>10</sup> and in the laboratory of Burnet in Melbourne.<sup>11</sup> As has already been mentioned the infection of a laboratory worker with the virus of the American strain of *Rickettsia burneti* led to the experiments by Dyer<sup>6</sup> which suggested the identity of this American infection with that which had been reported in Australia.

A further advance in our knowledge of the clinical course of the disease in man arose from a study of 15 cases of Q fever which developed in one building of the National Institute of Health in Washington in the spring of 1940. Hornibrook<sup>12</sup> entitled his report on this outbreak as "An Institutional Outbreak of Pneumonitis." Apparently the clinical symptoms in these patients were very similar to those reported originally by Derrick. The onset in all the cases was sudden, often with chilly sensations and general malaise. Headache of a severe and persistent character was an outstanding symptom. Chills and sweats were not uncommon. A few patients developed a short, hacking cough, but in none was it productive of a rusty sputum and aside from vague neuralgic-like chest pains, there were no other symptoms to indicate pulmonary involvement, nor were distinctive physical signs present on examination of the lungs. Nevertheless, roentgen-ray examination of the chest gave consistent evidence of pulmonary lesions. Soft infiltrative types of lesions, sometimes single but often multiple, were seen in the films. The densities were described as being of a more patchy type than is observed in the usual bronchopneumonia and less uniform in density than the shadows derived from lobar pneumonic involvement. Sputum examination showed no typical pneumococci. Mice injected with sputum were negative for the pneumococcus; and sulfapyridine did not exert any specific effect upon the pulmonary lesions nor upon the course of the disease. The disease in these cases was of varying severity, but in one instance proved fatal. Dyer, Topping and Bengtson<sup>13</sup> studied the outbreak from the point of view of the causative agent and were able to report upon the demonstration of *Rickettsia burneti* in three out of four cases in which procedures to effect this isolation were carried out. These authors pointed out the similarity of the clinical course and of the roentgenological findings in these cases with the descriptions of a non-pneumococcic pulmonary infection which had been described in the United States during the years 1935 to 1940 by various authors under the names of "atypical pneumonia," "pneu-

<sup>10</sup> SMITH, D. J. W., BROWN, H. E., and DERRICK, E. H.: A further series of laboratory infections with the *Rickettsia* of "Q" fever, Med. Jr. Australia, 1939, i, 13-14.

<sup>11</sup> BURNET, F. M., and FREEMAN, M.: Note on a series of laboratory infections with the *Rickettsia* of "Q" fever, Med. Jr. Australia, 1939, i, 11-12.

<sup>12</sup> HORNIBROOK, J. W., and NELSON, K. R.: An institutional outbreak of pneumonitis. I. Epidemiological and clinical studies, Pub. Health Rep., 1940, iv, 1936-1944.

<sup>13</sup> DYER, R. E., TOPPING, N. H., and BENGTSON, I. A.: An institutional outbreak of pneumonitis. I. Isolation and identification of causative agent, Pub. Health Rep., 1940, iv, 1945-1954.

monitis," "broncho-pneumonia of unknown etiology," etc. The discovery of inapparent pneumonitis as a characteristic feature of Q fever in man marks the opening of a new era in the recognition of this disease entity.

Though the infections in laboratory workers cited above added to the clinical picture of the disease in man, they did nothing to elucidate the mode of transmission of this infection to the human. In the case of the outbreak in the laboratory of Burnet in Melbourne, ecto-parasites of the laboratory mice were suspected as vectors but no conclusive proof was adduced. Similarly, a careful epidemiological study of the infection in the personnel in the National Institute of Health did not throw any light on the mode of their infection. However, Derrick, Smith, Brown and Freeman had carried on investigations as to the occurrence of the disease in animals in their natural state and in 1939 published a report<sup>14</sup> in which they demonstrated that the bandicoot, *Isodon torosus*, "a common, small animal in the Australian bush," was susceptible to the disease when inoculated with infective material, and moreover, that of 44 bandicoots tested before inoculation, four were shown to possess immune bodies to the virus of Q fever in the form of serum agglutinins against the *Rickettsia burneti*.

Having obtained evidence that the disease occurred in bandicoots in nature, it was a natural next step for the Australian investigators to search for a tick vector. Smith and Derrick<sup>15</sup> in 1939 reported the isolation of six strains of *Rickettsia burneti* from the tick *Haemaphysalis humerosa*. This tick is one of the common ecto-parasites of the bandicoot. The ticks were collected from bandicoots on Moreton Island, ground up in a mortar and the emulsion injected intraperitoneally into guinea pigs. Infection of the guinea pigs occurred. The homology of the tick-strains with strains of human origin was confirmed by their characteristic behavior during animal passage. The strains obtained in guinea pigs were transferred to mice in which typical rickettsia were demonstrated. The authors noted that the *Haemaphysalis humerosa* had been reported as occurring in a variety of host animals along the eastern and northern seaboards of Australia. There was record of its having been found on cattle. The authors were able to show that though *H. humerosa* had not previously been observed to attack man, they were able to induce it to feed on man under experimental conditions in the laboratory. They point out, however, that the significance of this naturally infected tick in the epidemiology of Q fever is not clear since a history of tick bite is not a feature of the human infection. A further paper by Derrick and Smith<sup>16</sup> in 1940 reported the isolation of three strains of *Rickettsia burneti* from the bandicoot, thus establishing definitely the occurrence in nature of a host ani-

<sup>14</sup> DERRICK, E. H., SMITH, D. J. W., and BROWN, H. E.: The role of the bandicoot in the epidemiology of "Q" fever: a preliminary study, Med. Jr. Australia, 1939, i, 150-155.

<sup>15</sup> SMITH, D. J. W., and DERRICK, E. H.: Studies in the epidemiology of "Q" fever. I. The isolation of six strains of *Rickettsia burneti* from the tick *Haemaphysalis humerosa*, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 1-8.

<sup>16</sup> DERRICK, E. H., and SMITH, D. J. W.: Studies in the epidemiology of "Q" fever. II. The isolation of three strains of *Rickettsia burneti* from the bandicoot *Isodon torosus*, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 99-102.

mal and a vector arthropod parasite. Further work reported by Smith<sup>17</sup> indicated that larval, nymphal and adult stages of the tick could be infected with rickettsia by feeding them upon infected guinea pigs during the febrile period. Smith showed, moreover, that the feces of infected ticks were highly infectious, being capable of infecting guinea pigs when applied either to abraded or unabraded skin.

Utilizing as an indication of infection the presence in serum of agglutinins for an emulsion of *Rickettsia burneti*, epidemiological surveys<sup>18</sup> were conducted. The first human survey was made at the Brisbane abattoir, where the original cases of Q fever had been discovered. Of 79 sera tested, 18 were found to show agglutination. Of these 12 had either had an attack of Q fever previously or a suspicious febrile illness not so diagnosed. In six instances, however, the individuals concerned were not aware of having had any fever. Similar positive agglutination tests were found in other workers and led the authors to the conclusion that Q fever may occur as an inapparent infection in the human.

An interesting observation was recorded in connection with the testing of cattle sera on a dairy farm, the owner of which had had Q fever himself six months previously. One of the 24 cow sera tested was completely positive.

The surveys on bandicoot sera showed a very high percentage of infected animals on Moreton Island. This was of interest in that 180 militia who encamped for training on this island did not in a single instance develop at a later date agglutinins for *Rickettsia burneti*. This result was taken to indicate that the tick *H. humerosa*, the common ecto-parasite of the bandicoots on Moreton Island, does not readily attack man and probably is not a common cause of direct human infection. The Australian group<sup>19</sup> of investigators tested nine species of bush animals apart from the bandicoot for susceptibility to Q fever and found that seven rodents and two marsupials were all susceptible upon inoculation. The failure to establish connection between the infected bandicoots and their infected ecto-parasites and human infections naturally led to renewed attention to other possible modes of transmission of the disease. The study<sup>20</sup> of the occupation and geographical distribution of Q fever patients in Australia showed that nearly all patients who lived in the country were associated with cattle and that practically all of the city patients in Brisbane worked at the meat works. In 1942 Derrick, Smith and Brown<sup>20</sup> demonstrated that calves were susceptible to inoculations with

<sup>17</sup> SMITH, D. J. W.: Studies in the epidemiology of "Q" fever by the tick *Haemaphysalis humerosa*, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 103-118.

<sup>18</sup> FREEMAN, M.: Studies in the epidemiology of "Q" fever. V. Surveys of human and animal sera for *Rickettsia burneti* agglutinins, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 193-200.

<sup>19</sup> DERRICK, E. H., SMITH, D. J. W., and BROWN, H. E.: Studies in the epidemiology of Q fever. VI. The susceptibility of various animals, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 409-413.

<sup>20</sup> DERRICK, E. H., SMITH, D. J. W., and BROWN, H. E.: Studies in the epidemiology of Q fever. IX. The role of the cow in the transmission of human infection, Australian Jr. Exper. Biol. and Med. Sci., 1942, xx, 105-110.

Q fever virus, and that after a brief illness so induced, the virus could be again isolated from the tissues. Cattle ticks were fed on one of the calves and some of these ticks became infected as demonstrated by guinea pig inoculation. The feces from such ticks contained *Rickettsia burneti*. Agglutinins for the *Rickettsia burneti* were found in the sera of 12 out of 879 dairy cattle in the Q fever endemic area. The authors concluded that it was likely that the cow becomes infected from the animal reservoir by means of ticks and that they can then transmit the infection to humans either directly from their tissues or indirectly from the crushed tissues or feces of their tick.

In the United States during the period of the above cited epidemiological investigations in Australia, work was proceeding on methods of growing the *Rickettsia burneti*. From the infected yolk sacs of developing chick-eggs abundant rickettsial material was obtained.<sup>21</sup> An adequate complement-fixation technic was developed for the serological separation of the rickettsial agents of endemic typhus, Q fever and Rocky Mountain Spotted Fever.<sup>22</sup> Complement fixation has proved a highly useful diagnostic tool in the later investigations on outbreaks of Q fever in different parts of the world.

Prior to entry of America into World War II, interest in Q fever was confined largely to those particularly concerned with investigations into the various forms of rickettsial disease. Developments during the war and after, however, have shown that this entity has a wider significance to the internist and general practitioner. During the winter and spring of 1944 to 1945 there occurred eight outbreaks of a febrile disease which closely resembled primary atypical pneumonia among allied troops in Italy, Greece and Corsica.<sup>23, 24</sup> Certain clinical, epidemiological and laboratory features were noted in these outbreaks which led to a more active investigation of the etiologic agent concerned. In three of the outbreaks animal inoculations led to the recovery of a rickettsial organism which was eventually shown to be identical with *Rickettsia burneti*. In five further outbreaks satisfactory serum samples obtained from patients showed specific antibody against this rickettsial agent. In May and June of 1945 an outbreak occurred among troops in transit from southern Italy to Camp Patrick Henry, Virginia and other ports of debarkation in the United States.<sup>25</sup> A study of the cases occurring at Camp Patrick Henry by immunological methods showed that the disease in question was Q fever. Evidence was obtained that the Ger-

<sup>21</sup> COX, H. R.: The cultivation of *Rickettsia diaporica* in tissue culture and in the tissue of developing chick embryos, Pub. Health Rep., 1939, liv, 2171-2177.

<sup>22</sup> PLOTZ, H.: Complement-fixation in rickettsial diseases, Science, 1943, xcvi, 20-21.

<sup>23</sup> ROBBINS, F. E., and RAGAN, C. A.: Q fever in the Mediterranean area: report of its occurrence in allied troops. I. Clinical features of the disease, Am. Jr. Hyg., 1946, xlv, 6-22.

<sup>24</sup> ROBBINS, F. E., GAULD, R. L., and WARNER, F. B.: Q fever in the Mediterranean area: report of its occurrence in allied troops. II. Epidemiology, Am. Jr. Hyg., 1946, xlv, 23-50.

<sup>25</sup> FEINSTEIN, M., YESNER, R., and MARKS, J. L.: Epidemics of Q fever among troops returning from Italy in the spring of 1945. I. Clinical aspects of the epidemic at Camp Patrick Henry, Virginia, Am. Jr. Hyg., 1946, xlv, 72-87.

man troops in Greece had suffered with a clinically similar infection.<sup>26</sup> Dr. J. Caminopetros of the Pasteur Institute of Greece had isolated the strain in guinea pigs. When carried to the United States for study this strain was propagated in chick embryos and shown to contain rickettsiae similar to those of Q fever.

The epidemiological studies made in these outbreaks which involved many hundreds of cases did not add to the sum of knowledge concerning the mode of transmission of the infection to man. No natural hosts of the diseases were identified in the areas concerned, nor were any infected vectors discovered. It was shown that the outbreaks were often explosive in nature with a high attack rate among the bodies of troops concerned. It was concluded as a result of serological studies among the natives of the regions in which the troops were quartered that the disease was probably endemic in these areas. As noted by previous observers the presence of immune bodies in the sera of men who had not suffered from apparent infection indicated that mild and clinically asymptomatic cases probably occurred.

The clinical differentiation of Q fever from primary atypical pneumonia of unknown etiology was suggested by the marked lack of respiratory symptoms in Q fever, in spite of the presence of roentgenologically detectable areas of consolidation in the lungs; and likewise by the absence in Q fever of cold agglutinins which had been shown to be present in over 90 per cent of the cases of primary atypical pneumonia of unknown etiology. A high degree of infectiousness of the rickettsial agent was again demonstrated by an outbreak of 20 cases in the 15th Medical General Laboratory in which studies on the disease were being carried forward.<sup>27</sup> Further details concerning the roentgenological evidences of lung consolidation were obtained from the study of this large human material.<sup>28</sup> It was shown that the chest film taken on admission to the hospital was often clear, consolidation appearing for the first time on the third, fourth or in some cases as late as the sixth day of the disease. The patchy area of consolidation which then appeared was more commonly found in the lower than in the upper lobe. In some instances several lesions were present. The density was of a homogeneous ground-glass appearance. It was often very slow in resolution. Of 33 patients followed for an average of 22 days, only six had negative lung findings on roentgen-ray at the time of discharge from the hospital.

Shortly after the close of the war a serious outbreak of Q fever occurred again in the National Institute of Health.<sup>28</sup> Forty-seven cases were involved. In each instance the person had a history of having been in one building of the National Institute of Health within 24 days before the onset

<sup>26</sup> ROBBINS, F. C., RAGAIN, C. A., GAULD, R. L., RUSTIGIAN, R. et al: Q fever: a foreword. Introduction to a series of papers dealing with Q fever, *Am. Jr. Hyg.*, 1946, xlv, 1-5.

<sup>27</sup> ROBBINS, F. E., and RUSTIGIAN, R.: Q fever in the Mediterranean area: report of its occurrence in allied troops. IV. A laboratory outbreak, *Am. Jr. Hyg.*, 1946, xlv, 64-71.

<sup>28</sup> HUEBNER, R. J.: Report of an outbreak of Q fever at the National Institute of Health. II. Epidemiological features, *Am. Jr. Pub. Health*, 1947, xxxvii, 431-440.

of illness. In this building the Rickettsial Disease Unit of the Institute was located. In the same period as the human outbreak there occurred an outbreak of the disease in two guinea pig colonies in the same building. Huebner in reporting upon the epidemiological features of this outbreak drew attention to the unusual degree of resistance of the *Rickettsia burneti* to heat and to formalin. He also showed that there was a correlation between the dates of preparation in the Institute of yolk sac antigens and the probable dates of exposure in the human cases.

The first explosive outbreak of an acute febrile illness in the civilian population of the United States identified as Q fever occurred during the month of March in 1946 in Amarillo, Texas.<sup>29</sup> It appeared among the employees of a stockyard, a live-stock auction company and a nearby meat-packing plant. Among the total of 136 employees of these three establishments, there were 55 cases of Q fever with two deaths, an attack rate of 40 per cent. The clinical symptoms<sup>30</sup> in these cases were essentially the same as those described in the European epidemics and in the original cases in Australia. Roentgenographic evidence of pulmonary consolidation was obtained in the majority of hospitalized cases. Diagnosis by means of complement-fixation reaction indicated that the infection had occurred without clinical symptoms in some of the personnel.<sup>31</sup> From the serum of two cases in this epidemic *Rickettsia burneti* were isolated and identified.<sup>32</sup>

In August of 1946 another outbreak in a packing house in Chicago occurred with 30 cases affected.<sup>33</sup> In neither of these outbreaks was the epidemiological evidence obtained sufficient to indicate conclusively the mode of transmission of infection to the individual who came down with the disease. While in the majority of instances close contact with cattle and with their blood and organs in the killing rooms had been experienced there were other cases in which the degree of contact was quite remote.

In the preceding account of the development of our knowledge of Q fever prior to 1947, it will have been noted that the disease in human beings has occurred in the form of outbreaks in meat packing plants, in laboratories working with the disease and in units of military personnel. In addition, however, mention has been made of sporadic cases occurring in the coastal area of northeastern Australia, in Greece and in Italy. It might be added

<sup>29</sup> TOPPING, N. H., SHEPARD, C. C., and IRONS, J. V.: Q fever in the United States. I. Epidemiological studies of an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 813-815.

<sup>30</sup> IRONS, J. V., and HOOPER, J. M.: Q fever in the United States. II. Clinical data on an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 815-818.

<sup>31</sup> IRONS, J. V., MURPHY, J. N., and WOLFE, D. M.: Q fever in the United States. III. Serologic observations in an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 818-820.

<sup>32</sup> COX, H. R., TESAR, W. C., and IRONS, J. V.: Q fever in the United States. IV. Isolation and identification of *Rickettsia* in an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 820-821.

<sup>33</sup> SHEPARD, C. C.: An outbreak of Q fever in a Chicago packing house, Am. Jr. Hyg., 1947, xlv, 185-192.



that such sporadic cases have likewise been observed in Panama, Switzerland and in Germany.

In the United States, however, prior to 1947 no true endemic area of Q fever had been detected. Since the spring of 1947, however, well over 150 cases have been detected and serologically proven in southern California, in an area including Los Angeles, Ventura, Santa Barbara and Orange Counties.<sup>34, 35</sup> Intensive work on the disease has been in progress in this area in the Q Fever Laboratory which was established in September, 1947 as a coöperative undertaking of the National Institute of Health, the California State Department of Public Health and the Los Angeles County Health Department. It has been found that proximity to dairies by reason of occupation or residence was a common factor in the histories of a large percentage of these cases. This led to intensive study of the cow as a factor in the transmission of the disease. A serological survey of over 2000 cows in Los Angeles County disclosed that approximately 13 per cent possessed serum antibodies against Q fever. It is of interest that less than 2 per cent of calves and bulls tested yielded serum reaction indicative of Q fever. Demonstrable illness in the reacting animals was absent. It proved impossible to recover the rickettsia of Q fever from the blood, the urine or the feces of the infected cows. On the other hand, when raw milk from the cows was tested, positive results in a high proportion of cases were at once obtained. These rickettsia were identified as identical with the *Rickettsia burneti* by morphological and all immunological reactions. It was found that pasteurization by acceptable methods sterilized the rickettsia-infected milk. This significant discovery has, however, not solved the problem of transmission of the disease from the cow to the human. The epidemiological investigations have clearly indicated that in a major proportion of the human cases the drinking of raw milk could not be incriminated as the cause of the transmission of the disease. It is evident, however, that inapparent infections of Q fever in cows are probably of great importance in the infection chain of Q fever.

It is believed by many that the widespread surveys now in progress in which there is being employed an antigen for complement-fixation studies which is more sensitive than that employed in earlier years, will result in the discovery of other endemic foci of Q fever in the United States. The disease is of growing importance to the practicing physician. It should be considered along with influenza, pulmonary tularemia, psittacosis, coccidioidomycosis, histoplasmosis and primary atypical pneumonia in determining the diagnosis in that puzzling group of patients who in addition to fever and malaise show a pulmonic consolidation for which no bacterial organism can be incriminated as the etiologic agent.

M. C. P.

<sup>34</sup> HUEBNER, R. J., JELLISON, W. L., BECK, M. D., PARKER, R. R., and SHEPARD, C. C.: Q fever studies in southern California, Pub. Health Rep., 1948, lxiii, 214.

<sup>35</sup> MEYER, H. F.: The animal kingdom, a reservoir of human disease, Ann. Int. Med. In press.

## REVIEWS

*Essentials of Endocrinology*. 2nd Ed. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P. 644 pages; 16 × 24 cm. J. B. Lippincott Company, Philadelphia. 1947. Price, \$10.00.

This is the second edition of a book which first appeared in 1941. In the preface, the author states that he has attempted to develop the subject on the basis of scientific background rather than on purely clinical concepts.

Endocrinology is a field which has developed rapidly and which is intimately related to a number of diseases which are fundamentally non-endocrine. Accordingly, it is difficult in a book of this size adequately to present the numerous ramifications of aberrations in function of the various glands.

The endocrine glands are considered from the standpoint of their structure, their function and the various clinical disorders which derive from altered physiology. The author advocates the use of anterior pituitary extracts in treating panhypopituitarism, the unitarian theory of adrenal cortical hormones, iodine therapy for simple goiter. These and other statements will be questioned by many.

The references are adequate, the illustrations are helpful and the format of the book is excellent.

J. Z. B.

*The Peripheral Circulation in Health and Disease: A Study in Clinical Science*. By ROBERT L. RICHARDS, M.D., Rockefeller Fellow in Medicine; Formerly Assistant Physician, Neurovascular Unit, Gogarburn Hospital, Edinburgh. 153 pages; 17 × 27 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1946. Price, \$6.00.

This monograph presents an excellent review of the physiology of the peripheral circulation, particularly with reference to its interrelationship with the autonomic nervous system. Various pathologic entities are discussed, in addition to diagnostic measures.

The chapters on Peripheral Nerve Injuries and Immersion Foot Syndrome are particularly comprehensive and noteworthy, representing a valuable contribution to this problem.

Each chapter is well summarized and enhanced by a very comprehensive bibliography. This monograph also contains an excellent author and subject index.

G. H. Y.

*The Medical Writings of Anonymus Londinensis*. By W. H. S. JONES, Litt.D., F.B.A. 168 pages; 22 × 14 cm. Cambridge University Press, Macmillan Co., New York. 1947. Price, \$2.75.

In this book the writer gives the complete Greek text and translation of a Greek medical papyrus, whose code name is *Anonymus Londinensis*. It was written in the second century A.D. in the style of a student comparing various authorities and schools of thought. Anyone who enjoys reading Hippocrates will appreciate this fragment. The author accompanies it with brief, but scholarly essays on Greek thought and medicine, as well as a carefully documented introduction to this text. This book represents a real addition to the source material of Greek medicine.

H. W. N.

*Recent Advances in Endocrinology.* 6th Ed. By A. T. CAMERON. 443 pages; 13.5 × 21 cm. Blakiston Company, Philadelphia. 1947. Price, \$6.00.

This book continues to present a well chosen, well organized and well presented condensation of a number of significant articles on endocrinology. The author discusses the anatomy, function and clinical aberrations of the various endocrine glands. To the physician who desires to acquaint himself with the present scientific or clinical concepts of glandular disorders, it will prove highly valuable, and it will serve admirably as a reference to anyone interested in endocrinology.

*Modern Dermatology and Syphilology.* 2nd Ed. By S. WILLIAM BECKER, M.D., Clinical Professor of Dermatology, University of Chicago, and MAXIMILIAN E. OBERMAYER, M.D., Clinical Professor and Chairman of the Department of Dermatology, University of Southern California. 1017 pages; 18.5 × 26 cm. J. B. Lippincott Co., Philadelphia. 1947. Price, \$18.00.

This second edition of *Modern Dermatology and Syphilology* has been greatly enlarged and many new additions are to be found.

It is worthy of note that in the chapter on Dermatologic Diagnosis the authors have presented several means of fixing and staining tissue, one of which, the dioxan method, is relatively new and apparently quite satisfactory.

The formulary has been amplified to include a number of preparations not mentioned in the previous edition and the formulae have been given for all of the compounds listed.

The general text is quite comprehensive and the various clinical descriptions are supplemented by the use of numerous photographs most of which are excellent.

The general chapter on syphilis is acceptable provided that the individual bears in mind the fact that the methods of syphilo-therapy are continually changing and that, unfortunately, most of the material appearing in textbooks is somewhat dated as it leaves the press.

The authors have revised their chapter on tropical cutaneous diseases and have amplified it to cover some of the more common things seen in World War II.

This new edition is far superior to the previous work.

H. M. R., JR.

### BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Conference on Metabolic Aspects of Convalescence—Transactions of the Fifteenth Meeting.* Edited by EDWARD C. REIFENSTEIN, JR., M.D. 163 pages (loose-leaf); 23 × 14.5 cm. (paper-bound). Josiah Macy, Jr. Foundation, New York. Price, \$2.25.

*Coronary Heart Disease.* By A. CARLTON ERNSTENE, M.D., Chief of the Section on Cardiovascular Disease, Cleveland Clinic. 95 pages; 22.5 × 14.5 cm. 1948. Charles C. Thomas, Springfield, Illinois. Price, \$2.50.

*Crystalline Enzymes.* 2nd ed. By JOHN H. NORTHROP, MOSES KUNITZ and ROGER M. HERRIOTT. 352 pages; 24 × 16 cm. 1948. Columbia University Press, New York. Price, \$7.50.

*The Digestive Tract in Roentgenology.* By JACOB BUCKSTEIN, M. D., Assistant Professor of Clinical Medicine, Cornell University Medical College, etc. 889 pages; 26.5 × 18.5 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$16.00.

- Diseases of the Chest, Described for Students and Practitioners.* 2nd ed. By ROBERT COOPE, M.D., B.Sc., F.R.C.P., Hon. Physician, Royal Liverpool United Hospital (Liverpool Royal Infirmary), etc. With a Foreword by LORD HORDER. 541 pages; 22.5 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$7.50.
- Essentials of Fevers.* 2nd ed. By GERALD E. BREEN, M.D., B.Ch. (N.U.I.Dub.); D.P.H., D.O.M.S. (R.C.P.Lond., R.C.S.Eng.), Tempy. Divisional Medical Officer, Hospitals Division, the London County Council, etc. 351 pages; 19.5 × 13 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$4.50.
- Gardiner's Handbook of Skin Diseases.* 5th ed. Revised by JOHN KINNEAR, O.B.E., T.D., M.D., M.R.C.P. (Ed.), D.L., Lecturer in Disease of the Skin, St. Andrews University, etc. 250 pages; 19.5 × 13 cm. 1948. The Williams and Wilkins Company, Baltimore. Price, \$4.50.
- Interesting and Useful Medical Statistics.* Edited by WILLIAM H. KUPPER, M.D. 528 pages; 23.5 × 16 cm. 1948. William C. Brown Company, Dubuque, Iowa. Price, \$6.50.
- An Introduction to Dermatology.* 11th ed. Formerly by NORMAN WALKER, Kt., M.D., LL.D., F.R.C.P., and G. H. PERCIVAL, M.D., Ph.D., F.R.C.P.E., D.P.H. 11th Edition by G. H. PERCIVAL, Grant Professor of Dermatology, the University of Edinburgh, etc. 349 pages; 22 × 15 cm. 1947. The Williams and Wilkins Company, Baltimore. Price, \$9.00.
- An Introduction to Physical Methods of Treatment in Psychiatry.* 2nd ed. By WILLIAM SARGANT, M.A., M.B. (Cantab.), M.R.C.P., D.P.M., Physician, Maudsley Hospital, etc., and ELIOT SLATER, M.A. M.D. (Cantab.), F.R.C.P., D.P.M., Physician in Psychological Medicine, National Hospital, Queen Square, etc. With a Chapter on Treatment of the Epilepsies by DENIS HILL, M.B. (Lond.), M.R.C.P., D.P.M., Physician in Psychological Medicine, King's College Hospital, etc. 215 pages; 22 × 14 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$3.50.
- Laboratory Diagnosis of Protozoan Diseases.* 2nd ed. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), D.Sc. (Hon.), F.A.C.S., F.A.C.P., Colonel, United States Army Medical Corps, Retired, etc. 384 pages; 24 × 15.5 cm. 1948. Lea & Febiger, Philadelphia. Price, \$6.50.
- Manual for Laboratory Work in Mammalian Physiology.* By FRED E. D'AMOUR and FRANK R. BLOOD. Loose-leaf, unnumbered pages; 21.5 × 28 cm. 1948. University of Chicago Press, Chicago. Price, \$2.75.
- Medical Research in War: Report of the Medical Research Council for the Years 1939-1945.* Committee of Privy Council for Medical Research—Presented by the Lord President of the Council to Parliament by Command of His Majesty, December, 1947. 455 pages; 24.5 × 15.5 cm. (paper-bound). 1948. H. M. Stationery Office, London. Price, 7s. 6d. net.
- The 1947 Year Book of Pathology and Clinical Pathology.* Pathology edited by HOWARD T. KARSNER, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University. Assistant Editor: HERBERT Z. LUND, M.D., Assistant Professor of Pathology, Western Reserve University. Clinical Pathology edited by ARTHUR HAWLEY SANFORD, M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation), etc. 558 pages; 18.5 × 12.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, \$3.75.

- Physiological Therapy in Respiratory Diseases.* 2nd ed. By ALVAN L. BARACH, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons, etc. 408 pages; 24 × 15.5 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$9.00.
- Psychiatry in a Troubled World: Yesterday's War and Today's Challenge.* By WILLIAM C. MENNINGER, M.D., General Secretary, The Menninger Foundation, Topeka, Kansas, etc. 636 pages; 24.5 × 16 cm. 1948. The Macmillan Company, New York. Price, \$6.00.
- Temporary Rise in the Frequency of Thyrotoxicosis in Denmark, 1941-1945.* By KURT IVERSEN. 244 pages; 25.5 × 17.5 cm. 1948. Rosenkilde and Bagger, Copenhagen. Price, Dan. Cr. 15.
- Treatment of Heart Disease.* By WILLIAM A. BRAMS, M.S., M.D., Ph.D., Associate Professor of Medicine, Northwestern University Medical School, etc. 195 pages; 24 × 15.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$3.50.
- War, Politics, and Insanity.* By C. S. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (Eng.). 121 pages; 21 × 13.5 cm. 1948. The World Press, Inc., Denver. Price, \$2.00.

## COLLEGE NEWS NOTES

### RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949–June 30, 1950. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for proper pursuit of his work. The stipend will be from \$2,200 to \$3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

---

### THE AMERICAN COLLEGE OF PHYSICIANS ESTABLISHES THE A. B. BROWER TRAVELING SCHOLARSHIP

At the San Francisco Annual Session of the College, the Board of Regents on April 18, through the generosity of Dr. A. B. Brower of Dayton, Ohio, who made a subscription of \$10,000, established "The Dr. A. B. Brower Traveling Scholarship Fund," which according to the conditions of the gift provide that "the income shall be used for the payment of expenses, in whole or part, of a deserving and promising young physician for attendance for a short period of time, for observation and study, at an outstanding institution of medical teaching, research or practice, such beneficiaries to be chosen and such institutions to be designated from time to time by the Board of Regents of the College." It is anticipated that a beneficiary will be selected annually, provided a suitable candidate can be selected and provided adequate income is available. The Committee on Fellowships and Awards will consult with the beneficiary as to the institution to be attended by him and the work which he especially desires to observe. It is felt that through the instrumentality of the College and its Committee on Fellowships and Awards exceptional opportunities may be provided not otherwise available to young men.

---

### ELECTIONS TO THE AMERICAN BOARD OF INTERNAL MEDICINE

The Board of Regents of the American College of Physicians has re-appointed for a term of three years Dr. Alex. M. Burgess of Providence, R. I., and Dr. Truman G. Schnabel of Philadelphia, Pa. Dr. Chester M. Jones of Boston, Mass., was also appointed to the Board for a term of two years, to fill out the unexpired term of Dr. William S. McCann, resigned.

At a recent meeting of the American Board of Internal Medicine Dr. Hugh J. Morgan, Nashville, Tenn., was elected Chairman, Dr. Marion A. Blankenhorn, Cincinnati, Ohio, Vice-Chairman, and Dr. Truman G. Schnabel, Philadelphia, Pa., was elected Secretary-Treasurer.

---

### DR. WESLEY W. SPINK APPOINTED ACTING GOVERNOR FOR MINNESOTA

Due to the illness of Dr. Edgar V. Allen, President Walter W. Palmer has appointed Dr. Wesley W. Spink, of Minneapolis, as Acting Governor of the College for the State of Minnesota, the appointment beginning as of June 1.

## COMMITTEE ON NOMINATIONS, 1948-49

In accordance with ARTICLE I, Section 3, of the By-laws, President Walter W. Palmer has appointed the following to serve on the Committee on Nominations for 1948-49:

Maurice C. Pincoffs (Regent), Baltimore, Md., *Chairman*  
A. B. Brower (Regent), Dayton, Ohio  
Harold H. Jones (Governor), Winfield, Kans.  
Chester S. Keefer (Governor), Boston, Mass.  
T. Homer Coffen (Fellow-at-large), Portland, Ore.

---

## SPECIALTY BOARD NOTICE

The American Board of Pediatrics, Inc., 718 Royal Union Bldg., Des Moines, Iowa; Lee F. Hill, M.D., Secretary-Treasurer. Examinations will be held in Seattle, Wash., September 10-12, and in Atlantic City, N. J., November 17-19, 1948. The written portion of these examinations will be held on July 30, 1948.

---

## UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL OFFERS POSTGRADUATE COURSES

Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California, announces the following courses offered in 1948:

*Diseases of the Chest*, given in collaboration with the American College of Chest Physicians and Stanford University School of Medicine; September 13 through 17; fee, \$50.

*Psychiatry and Neurology*, at the Langley Porter Clinic; full time, 12 weeks, August 30 through November 19; fee, \$200.

---

## A.C.P. COURSE IN GASTRO-ENTEROLOGY TO BE GIVEN AT UNIVERSITY OF CALIFORNIA AND STANFORD UNIVERSITY, SAN FRANCISCO

Drs. Theodore L. Althausen and Dwight L. Wilbur have agreed to organize and direct a course in Gastroenterology for the American College of Physicians at the Medical Schools of the University of California and Stanford University, San Francisco, during the week of February 7 to 12, 1949.

---

The Michael Reese Hospital Postgraduate School, Chicago, Ill., will offer an intensive postgraduate course in Electrocardiography under Louis N. Katz, M.D., M.D., F.A.C.P., August 16 to 28, 1948. Tuition will be \$150.00.

---

The University of California at Los Angeles will offer a course in the Application of Nuclear Physics to the Biological and Medical Sciences, August 2 to 20, 1948. The fee for the lecture series alone is \$100.00 and for the complete course, including laboratory training, \$350.00. Enrollment is limited and applicants must present biographical data for approval by an official committee. Among the subjects treated in this course are methods of measurement of radioactivity, production of radioactive substances, principles of radiochemistry, applications of radioactive tracers, biological, therapeutic and genetic effects of radiation, and health protection and safety.

Northwestern University Medical School will offer a 5-day orientation course in allergy under the sponsorship of the American Academy of Allergy, October 25 to 29, 1948, inclusive. The course will comprise a complete and practical coverage of the subject and will utilize teachers not only from Northwestern University, but also from other medical schools. For particulars direct communications to Department of Allergy, Northwestern University Medical School, Chicago.

---

The Council on National Emergency Medical Service of the American Medical Association met in Chicago on April 5 and 6, 1948, with Ernest E. Irons, M.D., F.A.C.P., representing the American College of Physicians. More than 125 representatives of medical societies, national health and disaster groups and the armed services were present. Among the subjects discussed were medical implications of modern warfare, rôle of military and civilian groups and the need for services and physicians. In response to the request of the Army, Navy and Air Force for the Council's advice with respect to the needs for expanding the medical program of the Services and preparing for possible emergency contingencies, the Council recommended a six-point program as follows: 1. A single medical examination for screening, induction and assignment of selectees; 2. Withholding of induction of medical officers until actually required for medical care of military patients; 3. Adoption by the Services of a similar relationship with civilian medical facilities and personnel in the United States to that which is accomplished by the Veterans Administration's medical program; 4. Equal status for civilian medical reserve officers and career medical officers; 5. Continuation throughout the emergency of medical education and essential research; 6. Establishment of a National Emergency Medical Board as an agency of the National Security Resources Board.

In a survey it was found that only seven states had active programs for disaster relief. Efforts will be made to stimulate action in this respect.

The Council went on record as opposing proposed legislation to induct physicians by compulsion of law into the armed forces. The Council also affirmed that, in view of the possibilities of modern weapons, it would be unsafe to lower the ratio of civilian physicians to the 1-to-1500 ratio which was reached in the last war.

---

#### OBSERVATIONS ON POSTGRADUATE COURSE No. 5, INTERNAL MEDICINE, WASHINGTON, D. C., MAY 17-22

The course in Internal Medicine was held at the Gallinger Municipal Hospital under the Directorship of Dr. Wallace M. Yater, F.A.C.P. Eighty-seven enrollees appeared for the course. All of the instructors appeared and gave their appointed lectures. The panel on Postwar Problems of Tropical Diseases, under Dr. Thomas A. Heidicke as moderator, was unusually interesting because of the presence of the following guest speakers: Dr. P. C. Sen-Gupta of Calcutta, India; Dr. Hamilton H. Anderson of San Francisco, Calif.; Dr. B. G. Maegraith of Liverpool, England; and Dr. Henry A. Meleney of New York City.

Ward rounds were made on the last afternoon and a question period was arranged at the end of most of the lectures. A new experiment in the course this year was the holding of an informal quiz on coronary heart disease at the end of one of the sessions. The men were so interested that they remained long after the appointed closing hour. Such informal quizzes prove extremely profitable. It is also desirable to have a larger proportion of clinical teaching and the Director expresses the intention of extending this type of teaching in future courses offered for the College. A smoker and reception was held at the end of the first afternoon session for the purpose of getting the group acquainted.



## VETERANS ADMINISTRATION APPROVES ACP COURSES

The Department of Public Instruction of Pennsylvania, which is the official approving agency for the Veterans Administration in that State, has issued official approval of all postgraduate courses offered by the American College of Physicians on its autumn, 1948 schedule. This approval, however, covers veterans residing in the State of Pennsylvania, and it should facilitate their collection of fees for these courses.

This approval does not affect other states than Pennsylvania, but the College may later obtain approval of the other states, so that members of the College from whatever state in which they live may enjoy the same privileges.

---

A.C.P. EDUCATIONAL COMMITTEES RECOMMEND GREATER DISSEMINATION OF  
INFORMATION AMONG PHYSICIANS CONCERNING THE MEDICAL  
ASPECTS OF RADIOACTIVITY

At a combined meeting of the Advisory Committee on Postgraduate courses and the Committee on Educational Policy of the American College of Physicians at the San Francisco Session during April, the following resolution was adopted: Resolved, The American College of Physicians shall encourage authorities in the field of radioactivity to prepare editorials which may be published in the ANNALS OF INTERNAL MEDICINE; that directors of various ACP courses be requested to schedule discussions by authorities on the use of isotopes; that the College explore further the development in this field through contact with already established courses, such as given by the Army, Navy, and certain of our universities; that the chairman of regional meetings be requested to schedule, when possible, lectures and/or demonstrations on the medical aspects of atomic energy.

---

FOURTH INTERNATIONAL CONGRESSES ON TROPICAL MEDICINE AND MALARIA,  
WASHINGTON, D. C., MAY 10-18, 1948

More than 1000 delegates from 44 countries attended the Fourth International Congresses on Tropical Medicine and Malaria which were sponsored by the United States Government through the Department of State. Joseph M. Hayman, Jr., M.D., F.A.C.P., Cleveland, participated in the Congresses as official representative of the American College of Physicians.

The Congresses included the following sections: Research and Teaching Institutes, Tropical Climatology and Physiology, Bacterial and Spirochetal Diseases, Virus and Rickettsial Diseases, Malaria, Helminthic Diseases, Protozoan Diseases, Nutritional Diseases of the Tropics, Tropical Dermatology and Mycology, Tropical Veterinary Medicine, Public Health, and Medical and Veterinary Entomology. While many of the papers presented consisted of reviews of work already published, several were reported to be of particular interest. Dr. H. E. Shortt described the demonstration of pre-erythrocytic stages of *P. cynomolgi* infection in the parenchymal liver cells of monkeys and similar findings in one case of *P. vivax* infection of man, establishing a long sought link in the history of malaria infection. Dr. A. S. Alving reviewed studies of pentamidine in the treatment of South Pacific vivax malaria. Concurrent administration of 0.010 gm. of pentamidine base and 0.33 gm. of quinine sulfate every 4 hours throughout the 24 hours, for 14 days, has reduced the relapse rate from 98 per cent after suppressive drugs to about 25 per cent, in experimental volunteers. Relapses were reduced to 2 per cent after a second therapeutic course.

Newer developments in the therapy of leprosy with the sulfones were discussed by Dr. Robert G. Cochrane, of India, and by Drs. F. A. Johansen, F.A.C.P., USPHS, and P. T. Erickson, USPHS. Chaulmoogra oil has been entirely abandoned in favor

of the sulfones, which are of low toxicity and may be administered safely enterally and parenterally. Bromine must be given intravenously whereas diasone and promizole have the advantage of being tolerated well orally. The sulfone drugs are not claimed to be specific remedies, nor are spectacular cures to be expected. Almost universal improvement has followed their use. Definite objective improvement, with reduction of bacilli in the leprous lesions and simple atrophy of the morbid anatomical changes in the skin and mucous membranes, does not appear until after three to six months.

Distinctly encouraging results in the treatment of filariasis were reported by the use of arsenamide and hetrazan.

Official languages of the Congresses were English, French and Spanish, and as papers were delivered they were translated into the other languages and heard by headphone and radio.

A special exercise on May 12 commemorated the demonstration by Walter Reed of the mosquito transmission of yellow fever. Major General Raymond W. Bliss, (MC), USA, F.A.C.P., opened the meeting, and Philip S. Hench, M.D., F.A.C.P., gave the address of the evening. In another special meeting the fiftieth anniversary of the discovery of the method of transmission of malaria by Ross was commemorated.

At the Plenary Session Leonard A. Scheele, M.D., F.A.C.P., Surgeon General of the U. S. Public Health Service, was elected President, and Colonel Charles F. Craig, (MC), USA, Ret'd, F.A.C.P., was elected an Honorary Vice-President.

---

#### ADDITIONAL LIFE MEMBERS

The College takes pleasure in announcing that by recent subscription the following Fellows became Life Members of the American College of Physicians: Edward A. Brethauer, Jr., Pittsburgh, Pa.; Harold H. Golz, Dhahran, Saudi Arabia; Theodore S. Heineken, Bloomfield, N. J.; Paul M. Rike, Pittsburgh, Pa.

---

A meeting of the Joint Committee for the Coördination of Medical Activities was held in Chicago on March 6, 1948. The American College of Physicians was represented by Dr. Walter L. Palmer, F.A.C.P., and Dr. Ernest E. Irons, F.A.C.P., both of Chicago. The latter serves as Chairman of the Committee. The discussions and actions taken at the meeting were fully reported in the Journal of the American Medical Association, May 15 issue.

---

At recent meetings, Euclid M. Smith, M.D., F.A.C.P., Hot Springs, Ark., was chosen President-Elect of the Arkansas Medical Society, and Charles H. Sprague, M.D., F.A.C.P., Bridgeport, Conn., was elected to the post of President-Elect of the Connecticut State Medical Society.

---

Esmond R. Long, M.D., F.A.C.P., Philadelphia, Pa., Director of the Henry Phipps Institute of the University of Pennsylvania and Director of Medical Research and Therapy of the National Tuberculosis Association, has been designated as Editor in Chief of the American Review of Tuberculosis. He succeeds in this position the late Max Pinner, M.D., F.A.C.P. Walsh McDermott, M.D., F.A.C.P., Associate Professor of Medicine in the Cornell University Medical School, has been appointed to the new position of Managing Editor of the Review. The editorial offices are being returned from Oakland, Calif., to New York City.

---

Dr. William B. Bean (Associate), of the University of Cincinnati College of Medicine, has been appointed Professor of Medicine and head of that Department at the State University of Iowa, Iowa City, assuming his duties on or about August 1, 1948. He succeeds the late Dr. Fred Smith, F.A.C.P.

Chester N. Frazier, M.D., Dr.P.H., F.A.C.P., Professor of Dermatology and Syphilology in the University of Texas School of Medicine and formerly of the Peiping Union Medical College, has been appointed Professor of Dermatology in the Harvard Medical School.

---

Alexander S. Wiener, M.D., F.A.C.P., Brooklyn, N. Y., has contributed to the College Library of Publications by Members a bound volume of his reprints of scientific articles.

---

James L. McCartney, M.D., F.A.C.P., Garden City, N. Y., has been elected President of a newly formed Nassau Neuropsychiatric Society which has been organized by private practicing neurologists and psychiatrists of Nassau County, N. Y.

---

Harold W. Kohl, M.D. (Associate), Tucson, was elected President of the Arizona State Medical Association at its annual meeting held recently in Phoenix. Robert S. Flinn, M.D., F.A.C.P., and Frank J. Milloy, M.D., F.A.C.P., both of Phoenix, were elected President-Elect and Secretary, respectively. Dr. Milloy also serves as Editor of Arizona Medicine.

---

Hyman I. Goldstein, M.D. (Associate), Camden, N. J., was official delegate of The National Gastroenterological Association and The New Jersey Gastroenterological Society to the Third National Congress on Cancerology which was held in Havana, Cuba, May 2-7, 1948. He was elected an honorary member of the Cuban Dermatological Society and a corresponding member of the Cuban Cancer Society. During his visit he delivered several papers before medical meetings.

---

A 16 mm., 3½ reel, sound motion picture in color entitled "The Role of Gastroscopy in the Diagnosis and Treatment of Gastric Pathology," has been produced for Leo L. Hardt, M.D., F.A.C.P., Clinical Professor, Department of Medicine, Loyola University School of Medicine. The film describes Dr. Hardt's studies of the human stomach, both normal and pathological, and the ability to follow the course of gastric pathology. With the aid of the gastroscope, Dr. Hardt and his associates have been able to develop a new anti-acid and to study the effect of this new anti-acid in the healing of gastric ulcers. The photography in this film is a combination of X-ray pictures indicating pathology with overlays of gastroscopic views of that pathology, the X-ray serving to locate points of infection. Inquiries concerning the film should be addressed to Harrower Laboratory, Inc., 920 E. Broadway, Glendale, Calif.

## OBITUARIES

## DR. GEORGE CHAMBERS ANGLIN

Dr. George Chambers Anglin died at his home in Toronto on April 14, 1948, from coronary thrombosis.

Dr. Anglin was born in Cork, Ireland, in 1890. He came to Canada in 1907 and graduated in Medicine from the University of Toronto in 1914. At the outbreak of World War I he was in England beginning post-graduate work but returned to Canada and joined the Royal Canadian Army Medical Corps. He was invalided home after three years of service and began the practice of internal medicine in Toronto. He became interested in pulmonary tuberculosis and respiratory diseases in general and joined the Chest Clinics of the Toronto Western Hospital and the Christie Street Military Hospital.

In World War II he became a consultant in diseases of the chest to M.D. 2 and to the Royal Norwegian Air Force in Toronto. He received the Haakon VII Medal of Liberation from the King of Norway in recognition of his services. At the time of his death, he was serving as Chief of the Chest Clinic of the Department of Veterans Affairs in Toronto.

Dr. Anglin became a Fellow of the American College of Physicians in 1931. He was a member of the Laennec and Trudeau Societies, the American Academy of Allergy, the American College of Allergists, the American College of Chest Physicians, and a diplomate of the American Board of Internal Medicine.

Possessed of a genial personality and impelled by a natural interest in people, Dr. Anglin was also endowed with unusual ability and as a result he reached a high level in the field of medicine and was a strong influence in the improvement of medical practice in this country.

H. K. DETWEILER, M.D., F.A.C.P.,  
Governor for Ontario

## DR. LOUIS H. BEHRENS

Dr. Louis H. Behrens was long a teacher of medicine in St. Louis and one of the prominent figures in the practice of internal medicine. He gave unsparingly of his time and energy to organized medicine in St. Louis and served as president of the St. Louis County Medical Society which was an important force in the education of the average doctor.

Born July 12, 1868, Dr. Behrens acquired the degrees of Ph.G. from the St. Louis College of Pharmacy in 1888, and of M.D. from the Missouri Medical College in 1894. He served on the staffs of the Missouri Medical College and the Barnes Hospital for many years. He held commission during World War I as Captain in the U. S. Army Medical Reserve Corps. Dr. Behrens became a Fellow of the American College of Physicians in 1924, and a diplomate of the American Board of Internal Medicine in 1937.

For many years prior to his death on January 1, 1948, he had been incapacitated but had retained his contact with medical interests. He outlived most of his associates and friends, but is still vividly remembered. He achieved a definite position in the estimation and affection of his surviving associates.

R. A. KINSELLA, M.D., F.A.C.P.,  
Governor for Missouri

# ABRIDGED MINUTES OF THE COMBINED EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS

SAN FRANCISCO, CALIF.

APRIL 18, 1948

The combined Executive Session of the Board of Regents and Board of Governors was called to order at 2:15 p.m. in Room 203 of the Civic Auditorium, San Francisco, Calif., Sunday, April 18, 1948, with President Hugh J. Morgan presiding, and Mr. E. R. Loveland acting as Secretary.

President Morgan announced that after the taking of the roll, the two Boards would conduct their proceedings by separate action, but invited the members of both Boards to participate in discussions. Roll call showed the following in attendance:

*Officers and Regents:* Hugh J. Morgan, *President*; Walter W. Palmer, *President-Elect*; Reginald Fitz, *First Vice President*; Francis G. Blake, *Second Vice President*; Charles T. Stone, *Third Vice President*; William D. Stroud, *Treasurer*; George Morris Piersol, *Secretary-General*; Walter B. Martin; William S. Middleton; James E. Paullin; LeRoy H. Sloan; George F. Strong; William S. McCann; T. Grier Miller; Charles F. Moffatt; Charles F. Tenney; David P. Barr; A. B. Brower; Alex. M. Burgess; Ernest H. Falconer; Cyrus C. Sturgis; Maurice C. Pincoffs, *Editor, ANNALS OF INTERNAL MEDICINE*; Walter L. Palmer, *Chairman, Board of Governors*.

*Governors:* E. Dice Lineberry, Birmingham, ALABAMA; Fred G. Holmes, Phoenix, ARIZONA; Lewis B. Flinn, Wilmington, DELAWARE; Turner Z. Cason, Jacksonville, FLORIDA; Samuel M. Poindexter, Boise, IDAHO; Morris Flexner, Louisville (ALTERNATE), KENTUCKY; Eugene H. Drake, Portland, MAINE; John G. Archer, Greenville, MISSISSIPPI; Ernest D. Hitchcock, Great Falls, MONTANA and WYOMING; Asa L. Lincoln, New York, NEW YORK (Eastern); Marion A. Blankenhorn, Cincinnati, OHIO; Homer P. Rush, Portland, OREGON; M. D. Levy, Houston, TEXAS; Karver L. Puestow, Madison, WISCONSIN; Harold A. Des Brisay, Vancouver, B. C. (ALTERNATE), ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN; Leland Hawkins, Los Angeles, CALIFORNIA (Southern); Ward Darley, Denver, COLORADO; Walter Weissenborn, Hartford (ALTERNATE), CONNECTICUT; WALLACE M. Yater, Washington, DISTRICT OF COLUMBIA; Cecil M. Jack, Decatur, ILLINOIS (Southern); Robert M. Moore, Indianapolis, INDIANA; Harold H. Jones, Winfield, KANSAS; Chester S. Keefer, Boston, MASSACHUSETTS; Joseph D. McCarthy, Omaha, NEBRASKA; Edward C. Reifenstein, Sr., Syracuse, NEW YORK (Western); Wann Langston, Oklahoma City, OKLAHOMA; Edward L. Bortz, Philadelphia, PENNSYLVANIA (Eastern); R. R. Snowden, Pittsburgh, PENNSYLVANIA (Western); John L. Calene, Aberdeen, SOUTH DAKOTA; William C. Chaney, Memphis, TENNESSEE; Louis E. Viko, Salt Lake City, UTAH; Harry L. Arnold, Honolulu, HAWAII; Arless A. Blair, Fort Smith, ARKANSAS; Dwight L. Wilbur, San Francisco, CALIFORNIA (Northern); Benjamin F. Wolverton, Cedar Rapids, IOWA; Edgar Hull, New Orleans, LOUISIANA; Douglas Donald, Detroit, MICHIGAN; Frank J. Heck, Rochester (ALTERNATE), MINNESOTA; Ralph A. Kinsella, St. Louis, MISSOURI; Lawrence Parsons, Reno, NEVADA; Harry T. French, Hanover, NEW HAMPSHIRE; A. J. V. Klein, Newark (ALTERNATE), NEW JERSEY; Verne S. Caviness, Raleigh (ALTERNATE), NORTH CAROLINA; W. E. G. Lancaster, Fargo (ALTERNATE), NORTH DAKOTA; Robert Wilson, Jr., Charleston, SOUTH CAROLINA; Ellsworth L. Amidon, Butlington, VERMONT; Charles M. Caravati, Richmond, VIRGINIA; George Anderson, Spokane, WASHINGTON; Delivan A. MacGregor, Wheeling, WEST VIRGINIA; Arthur T. Henderson, Montreal, QUEBEC; George C. Beach (ALTER-

NATE), UNITED STATES ARMY; John Harper (ALTERNATE), UNITED STATES NAVY; G. A. Abbott (ALTERNATE), UNITED STATES PUBLIC HEALTH SERVICE.

*Guest:* William J. Kerr, Co-General Chairman, San Francisco Session.

The Secretary read abstracted Minutes of the preceding meeting of the Board of Regents, which were approved as read.

President Morgan called upon the Secretary to present communications, as follows:

(1) A letter from Dr. A. B. Brower, Regent, of Dayton, Ohio, tendering a donation of \$10,000.00 for the founding of a traveling fellowship in medicine, the income from which shall be used for the appointment annually of a deserving and promising young physician for attendance for a short period of time, for observation and study, at an outstanding institution of medical teaching, research or practice, the beneficiary to be chosen and the institution to be designated from time to time by the Board of Regents of the College.

. . . On motion by Dr. James E. Paullin, seconded by Dr. George Morris Piersol, a resolution was adopted, accepting the gift with the greatest appreciation, "a very substantial and practical stimulus to the attainment by the College of one of its important missions and purposes." . . .

(2) A notice from the American Board of Internal Medicine to the effect that the following appointees' terms, by the Board of Regents of the American College of Physicians, to the American Board of Internal Medicine will expire on June 30, 1948, and that new appointments shall be made:

Dr. Truman G. Schnabel

Dr. Alex. M. Burgess

Also, due to the resignation of Dr. William S. McCann, as of June 30, 1948, a new appointee should be nominated for his unexpired term, to June 30, 1950.

. . . President Morgan requested that the Committee on Educational Policy, headed by Dr. William S. Middleton, Chairman, bring to the next meeting of the Board of Regents names of nominees for these three vacancies. . . .

(3) A letter of appreciation from the Secretary of the Regents of the University of Wisconsin, stating that the fees amounting to \$1,975.00, transmitted by the College to the University of Wisconsin, covering a recent Postgraduate Course under the direction of Dr. William S. Middleton, had been accepted by the Regents of the University and credited to the Medical Library Building Fund.

(4) A report that President Hugh J. Morgan had appointed Dr. William S. McCann as representative of the College at ceremonies in Rochester, N. Y., January 12, 1948, in connection with the Regional Blood Program of the American Red Cross.

(5) A report of the appointment by President Hugh J. Morgan of Dr. George Morris Piersol, as College representative, on the Executive Committee of the President's Committee on "National Employ the Physically Handicapped Week."

(6) A letter from Dr. Paul R. Hawley, resigning from the College Governorship of the Veterans Administration, concurrent with his retirement as Medical Director of that Service, and announcement of the interim appointment by President Hugh J. Morgan of Dr. Arden Freer as Governor for the Veterans Administration.

(7) An announcement of the appointment of Dr. Ernest H. Falconer as College representative to the Pacific Regional Conference of UNESCO.

(8) An announcement of the appointment by President Hugh J. Morgan of Dr. Walter W. Palmer and Dr. George Morris Piersol as College representatives on the First International Poliomyelitis Conference.

(9) An announcement of the appointment by President Hugh J. Morgan, by authorization of the Board of Regents, of a Committee to consult with the Committee of the American Medical Association, the American College of Surgeons, and hospital

associations, concerning means by which nursing education and other services may be furthered, the Committee of the College consisting of Dr. Francis G. Blake, Chairman, Dr. Walter W. Palmer and Dr. Thomas P. Murdock.

(10) An announcement of the appointment by President Hugh J. Morgan of Dr. Ernest E. Irons as College representative to attend a two-day meeting of the Council on National Emergency Medical Service, April 5-6, at Chicago, and to bring any matter of importance to the Regents at San Francisco.

... (Dr. Irons was absent at the Regents' meeting, and there was no report.) ...

PRESIDENT HUGH J. MORGAN: The reports relative to the above appointments have been received and filed, or will be received for review if there are any matters that need the attention of the Regents at a subsequent meeting. We shall refer the resignation of Dr. Paul R. Hawley to the Committee on Nominations, so that a permanent successor may be nominated at the proper time.

The next item will be a report from Co-Chairmen Kerr and Falconer on the San Francisco Session.

DR. WILLIAM J. KERR: On behalf of the Fellows, Regents and Governors in California and all the Western States, we welcome you to San Francisco. We think we have a good program, some entertainment that will please you. Beginning tonight there will be some entertainment at the combined dinner of the Regents and Governors; there will be a Symphony Concert tomorrow night. The scientific program is, we believe, an excellent one, with morning lectures, panel discussions, clinics, inspection tours, general sessions, etc. We expect to give you some real live clinics, and we have arranged the programs so that morning lectures and clinics will not conflict. We open our arms to you and bid you welcome.

DR. ERNEST H. FALCONER: ... If there is anything any of you want to do not listed on the program, just make your wishes known to me and I shall try to fulfill them while you are here.

PRESIDENT MORGAN: On behalf of the Governors and Regents, I think this is the appropriate time to express our thanks to Dr. Kerr and Dr. Falconer for arranging what is obviously going to be an outstanding meeting of the College.

We shall now receive the report of the Secretary-General, Dr. George Morris Piersol.

... Dr. Piersol reported that since the last meeting of the Board of Regents there had been recorded the deaths of 43 Fellows and 5 Associates, whose names were spread upon the Minutes; also that since the last meeting of the Board 78 additional Fellows have become Life Members, making a grand total of 708, of whom 51 are now deceased, leaving a balance of 657. The names of these new Life Members were, likewise, spread upon the Minutes. ...

... Special mention was made of the name of Dr. Samuel E. Munson, who had served a long time as the Governor of the College for southern Illinois; the members of the Board stood in silence in respect to the deceased members. ...

PRESIDENT MORGAN: May we now receive the Memorial on Dr. Fred W. Wilkerson, prepared by Dr. Walter B. Martin and Dr. Walter L. Palmer.

DR. WALTER B. MARTIN: This is in memoriam of Dr. Fred W. Wilkerson, and is in the form of a resolution:

"The Board of Regents of the American College of Physicians records with sorrow the loss of one of the distinguished members of the American College of Physicians, Dr. Frederick Wooten Wilkerson.

"Doctor Wilkerson, the son of a physician, exemplified the best in the traditions of our profession. His interests were broad and won him a place of high honor, not only in the strictly professional field, but as a leader in organized medicine. As President of his state society, a member of the House of Delegates of the American Medical Association, and as the representative of his State on the Board of Governors of the American College of Physicians for many years, he served the interests of our

profession, and of the general public. His life and works may well be an inspiration to those that come after him.

"The Board of Regents of the American College of Physicians therefore RESOLVES that this expression of our appreciation of his contributions to our profession and to society be spread on our permanent records, and that a copy be sent to his family."

PRESIDENT MORGAN: Next we shall receive a Memorial on Dr. Ernest B. Bradley, former Governor and former President, prepared by Dr. James E. Paullin and Dr. David P. Barr.

DR. JAMES E. PAULLIN: "WHEREAS, Ernest Brennan Bradley, A.B., M.D., M.A.C.P., who had served the American College of Physicians as a member of the Board of Governors, as a member of the Board of Regents, and as its President (1936-37), was called by death on November 12, 1947, and

"WHEREAS, Dr. Bradley was known to the members and in particular to the official family of the American College of Physicians as a leader in his profession, with unusual powers for organizing and promoting educational programs for the advancement of medical training and knowledge, and

"WHEREAS, his wisdom and farsightedness, together with his lovable attributes, stimulated and encouraged those with whom he was associated, and

"WHEREAS, during his term of office as President of the American College of Physicians, through his guidance and planning, the scientific meetings of the College were expanded in scope, and the usefulness of the College was broadened by the establishment of regional meetings, all of which evidenced his abiding faith in the position which the College must assume as a medium of promoting better medical care, now. THEREFORE, be it

"RESOLVED, that we, the members of the Board of Regents, being deeply conscious of the great loss in his death to the American College of Physicians, and to the medical profession of his state, deplore his passing, and that we record this tribute to his memory, and be it FURTHER

"RESOLVED, that a copy of these resolutions be transmitted to his family as evidence of our deep love and affection for him, and as an expression of our sympathy in their loss and bereavement."

PRESIDENT MORGAN: Next we shall receive a Memorial on Dr. John H. Musser, former Regent and former President, prepared by Dr. William S. Middleton and Dr. T. Grier Miller.

DR. WILLIAM S. MIDDLETON: "JOHN HERR MUSSER (1883-1947). In this day of professional materialism it is refreshing to review the career of a man whose life was dedicated to medicine. John Herr Musser, a Philadelphian by birth, was the son of an eminent clinician and the sixth in direct line in this profession. Had he set about to pursue his career upon the established chart of his remarkable heritage, he could not have steered a truer course.

"With a firm foundation of secondary education at the William Penn Charter School and of academic training in the College of the University of Pennsylvania, John Musser entered upon the study of medicine. His undergraduate medical work at the University of Pennsylvania School of Medicine marked him as a worthy successor to his medical forbears. His father was a distinguished Professor of Clinical Medicine in the University while he was pursuing his studies. Upon his graduation from the School of Medicine (1908), John Musser served his internship for six months at the University Hospital and two years at the Pennsylvania Hospital. Thereupon a short period of graduate study was spent at the University of Amsterdam. Returning to Philadelphia, he was associated with his father in the practice of medicine, until the latter's death (1912). Three institutions in Philadelphia, Howard Hospital, Philadelphia General Hospital and Presbyterian Hospital, gained greatly by his attendance upon the medical services. As Associate in Medicine (1914-20) and Assistant



Professor of Medicine (1920-24), John Musser gave unstintingly of his talents to undergraduate medical instruction in his Alma Mater. Under his direction new life was given to the Outpatient Service and teaching in the University Hospital. His normal career was interrupted by two years of military service in World War I. Nor did his interest in military medicine cease with the termination of hostilities. He maintained his Reserve Corps affiliation to become a colonel in 1938. However, the return to private practice in Philadelphia found the pace a killing one and the opportunities for independent effort and study limited by its exactions. Accordingly, John Musser left Philadelphia to become Professor of Medicine at Tulane University of Louisiana School of Medicine in 1924. His interest in Pennsylvania never waned. He served as a graduate representative on its Board of Trustees. In recognition of his services and of his eminence in medicine he was granted the Award of Merit by the University (1940).

"Arriving in New Orleans when forty-one years old, John Musser found certain challenges that only his tact, poise, and tenacity of purpose could have surmounted. His post was the first full-time professorship in a clinical field in a proud Southern university. Furthermore, internal medicine was not developed or practiced in the accepted sense of a specialty in any measure in New Orleans. Opposition in high places was inevitable. With characteristic imperturbability John Musser bent his unselfish energies to the task of creating one of the best departments of medicine in the United States. Soon his patent integrity and measured enthusiasm won increasing allegiance from the medical students and from the younger staff members. His background of clinical and laboratory research insured the firm foundation of his department at Tulane; but his profound human interest and keen clinical instinct held him close to the bedside, where his fine analytical mind found full expression and outlet in the training of young internists.

"John Musser was a big man in every sense of the word. His warm personality permeated every gathering to which he lent his presence. Yet he did not sacrifice his high principles to mere social advantage. When the lines were drawn in support of the health and well-being of the children of Louisiana, John Musser's position was clearly stated, even though the red herring of state medicine was aligned with the immunization program. Without thought of personal sacrifice he gave one-half of his time (1940-42) to assist in the reorganization of the Louisiana State Board of Health. As a fitting tribute to his effort in another cause the new unit for tuberculous patients at Charity Hospital had been named for him.

"John Musser early demonstrated a literary flair. Over one hundred and fifty medical articles came from his pen. In the main they dealt with clinical subjects; but his earlier contributions to the physiology and the pathology of the spleen are noteworthy. Significantly he made a special study of 'The Heart That Is Ageing.' His assistant (1911-20) and chief editorship (1920-24) of the American Journal of the Medical Sciences marked a season of remarkable growth in this standard periodical. Upon his transfer to Louisiana he became Editor of the New Orleans Medical and Surgical Journal (1927) and he served on the Editorial Board of the Archives of Internal Medicine for some years. His earliest venture in medical textbook publication was the editorship of four editions of his father's 'Practical Treatise on Medical Diagnosis.' After several further excursions into this field he undertook a major project in the publication of 'Internal Medicine, Its Theory and Practice' (1932), which ran through its fourth edition in 1945.

"Many medical organizations profited by John Musser's active participation in their scientific deliberations and administrative affairs. In addition to the local and regional societies to which he contributed so materially, he was active in the American Medical Association, the Association of American Physicians, the College of Physicians of Philadelphia, the American Clinical and Climatological Association, the American Society of Clinical Investigation, and the American College of Physicians.

In all candor it may be said that to none of these groups did he give more abundantly than to the American College of Physicians. His Fellowship in the College dated from 1920. He served as Regent from 1926 to 1936. He became President-Elect at the Twelfth Annual Clinical Session at New Orleans (1928) and President the following year. The College was experiencing a renaissance at the time and through the stabilizing influence of such men as John Musser came the implementation of earlier reform movements. John Musser strove for the consolidation of effort. Through an economy of existing agencies and personnel a three-fold objective of the College was fixed. In his judgment better standards of admission to Fellowship, rehabilitation of the educational program and improvement of the official organ of the College required immediate attention.

"In the evolution of the plans for the certification of internists John Musser's leadership and vision made him a logical nominee from the American College of Physicians for the formation of the original American Board of Internal Medicine. In its ultimate organization, however, it became expedient that his nomination come from the Section on the Practice of Medicine of the American Medical Association. In no other capacity did the fine statesmanly qualities of John Musser stand in better stead than in the organization and early operation of the American Board of Internal Medicine. The minutes of the meetings of this Board until the expiration of his third term of service (July 1, 1945) reflect the clarity of his vision and his keen interest in the advancement of American medicine. The composition of the Founders' Group, the policy of certification without examination, and the conduct of special examinations for candidates in the Armed Services assigned to overseas duty are a few marks of these qualities. Contemplative always John Musser would allow a discussion to pass without comment. Occasionally he would make a note and then with a fine analysis of the intricacies of the problem, for the first time he would offer his own opinion of the situation. In retrospect it is singular how frequently his motion or amendment carried.

"In the very nature of the man, it was inevitable that John Musser should have been so regularly sought in support of public works, both regional and national. His membership on many committees, lay and professional, commonly led to his chairmanship or presidency in the same. Yet never was there a feeling of aggression. His associates deferred to his natural leadership and unobtrusively John Musser took such responsibilities without offense to the participating members. His patent sincerity and integrity stilled all reservations. His qualities of friendship were as well developed as his talents of leadership. With fine sensitivity he avoided friction. His consideration for his fellowman was a measure of the secret wells of his strength. His humanity and profound interest in people led to personal sacrifices of time and energy he could ill afford. Yet always the kindly touch and the unaffected personal absorption in his associates made the occasion one of warm mutual understanding rather than a perfunctory issue. In the years when physical limitations were imposed by his growing infirmity, John Musser never lost his fine philosophy. He refused to bow to his handicap. In spite of a major disability he persisted in his manifold interests within the limits of his physical capacity until a second invader finally overwhelmed his stalwart body. Never did the stout spirit waver. His courage and fortitude sustained him to the end. Gentleman unafraid, teacher-clinician extraordinary, medical statesman supreme, Master of the American College of Physicians, John Musser will be a figure long remembered and revered in American medicine."

PRESIDENT MORGAN: These three Memorials are fine expressions of the feelings and admiration and affection that we hold in our minds and hearts for these great physicians and late fellow members of this College. The Regents and Governors are indebted to the authors for these Memorials.

We shall next have the report of the Committee on Credentials by Dr. George Morris Piersol, Chairman.

. . . Dr. Piersol reported the Committee on Credentials had held two meetings since the last meeting of the Board of Regents, the first on February 28, 1948, and the second on April 17, 1948. The report was long and detailed, and out of it grew the following actions: Dr. L. Clagett Beck, Honolulu, T. H., was granted an extension of his Associate term for a period of two years; Dr. Maxwell R. Berry, Jr., of Atlanta, Ga., and Dr. Edmund L. Shlevin, of Brooklyn, N. Y., were reinstated to Associateship, each for a term of one year. . . .

. . . Dr. A. B. Brower, a former Governor and at present a member of the Committee on Credentials, was requested to appear before the Board of Governors to explain the very effective plan he followed while Governor in investigating candidates for membership. The Committee recommended that special steps be taken to encourage the several Governors of the College to investigate candidates more thoroughly through other Fellows or Masters in their respective territories. . . .

. . . 104 Fellows and 195 Associates were elected (these names were published in the June, 1948, issue of this journal). . . .

. . . Of the candidates elected to Associateship five years previously, namely, April 4, 1943, and whose five-year terms, under normal circumstances, would expire during the spring of 1948, 30 had qualified for advancement to Fellowship; 26 had received extension of time, because of military service; and 9 had failed to qualify and were dropped from the Roster, in accordance with provisions of the By-Laws, and their names were recorded in the Minutes; also the names of the 26 physicians having extended Associate terms were recorded in the Minutes. In addition, the Committee recorded the names of 6 Associates who were elected prior to April 3, 1943, whose terms had previously been extended because of military service, but whose terms at this time expired without their qualifying for Fellowship, and they were consequently dropped. . . .

PRESIDENT MORGAN: This represents an extraordinary amount of work on the part of this Committee, work accomplished in the most careful fashion. We all desire to express our appreciation. A more important Committee cannot exist in this College.

We shall now have a report from the Committee on Constitution and By-Laws by Dr. James E. Paullin, Chairman.

DR. JAMES E. PAULLIN: The By-Laws of the College were amended at the 1947 Annual Session of the College, and, among other things, provided a new Article VI for the election of Masters, in which it is specified, "a special Committee on Masterships will be named by the President. This Committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring in nominations of Masters to the Board of Regents for election or rejection."

That amendment makes it necessary for an amendment to the Constitution, Article IV, (b), substituting in line 5, "Committee on Masterships" in the place of "Committee on Credentials." Namely, this paragraph shall be amended to read:

"Masters of the American College of Physicians shall be those who have attained the rank of Fellows, and who on account of personal character, positions of influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships to the Board of Regents for special and well-earned distinction. Such Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M.A.C.P. in connection with scientific publications, at professional and academic functions and in connection with their professional activities."

This amendment shall be submitted to the members at the next Annual Business Meeting at San Francisco, April 22, 1948, for approval.

. . . On motion duly made, seconded and carried, the above amendment to the Constitution was approved, with the recommendation that it be approved at the Annual Business Meeting for final change and correction. . . .

PRESIDENT MORGAN: Next will be the report of the Committee on Fellowships and Awards by Dr. Reginald Fitz, Chairman.

DR. REGINALD FITZ: As recorded in the Minutes of the previous meeting of the Board of Regents, this Committee nominated seven men for Research Fellowships, beginning July 1, 1948, and for this purpose \$20,460.00 was appropriated. At the time the Committee met it felt that in the event of any of the candidates being unable to accept the fellowship offered, the Committee would prefer not to make any substitute nominations, and any excess fund should be returned to the fellowship pool. Since the last meeting we have received word that one of our appointees, Dr. Joseph E. Giansiracusa, has decided not to accept the fellowship. Therefore, the Committee recommends that the \$3,200.00 thus released be returned to the fellowship pool.

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Alex. M. Burgess, the recommendations of Dr. Fitz were unanimously approved. . . .

PRESIDENT MORGAN: We shall now have the report of the House Committee by Dr. William D. Stroud, Chairman.

DR. WILLIAM D. STROUD: The new building project is essentially completed and is now occupied. The only remaining things to be done are the putting up of venetian blinds in the first and second floors, the installation of screens and the replanting of the lawn. Financial statement follows:

Original Contract (R. M. Shoemaker Co.) .....	\$47,980.00
Additions:	
1 Extra Radiator (Pindar's Office) .....	192.00
Removal of varnish and refinishing old woodwork, 1st floor .	375.00
Entrance, Basement .....	409.75
	<hr/>
	\$48,956.75*
Architect's Fee, 6% .....	2,937.41*
Other Additions:	
Electric Fixtures .....	413.42
Venetian Blinds and Shades .....	350.00
Screens .....	325.00
Landscaping (Plantings) .....	564.30
Rubber and Plastic Floorings .....	1,332.00
Refinishing Rear Stairs .....	275.00
	<hr/>
TOTAL CONTRACTED COST .....	\$55,153.88
APPROPRIATION .....	55,000.00
	<hr/>
DEFICIT .....	\$ 153.88

\* Payments during progress:

12-3-47 Contractor .....	\$20,277.00
1-1-48 Architect .....	1,919.20
1-1-48 Contractor .....	8,757.90
2-14-48 Contractor .....	7,938.00
3-11-48 Contractor .....	4,879.80
	<hr/>
TOTAL Paid to April 7, 1948 .....	\$43,771.90
Balance Due Architect .....	1,018.20
Balance Due Contractor .....	7,104.05

The whole addition is considered eminently satisfactory and fine, an addition to the Headquarters of which everyone will be proud. Of prime importance is the fact that the Executive Offices now have full and ample room for efficient work and adequate space for internal expansion over many years to come.

The entire staff is now organized on the first floor, with the exception of the Addressograph and Duplicating Departments, which are on the basement level. An excellent meeting room, with facilities to accommodate more than one hundred individuals, is on the second floor. It is anticipated that this room may be used for Regional Meetings, Postgraduate Courses, and other purposes. There appears no immediate need to consider the purchase of suitable chairs for this meeting room until autumn, or at the pleasure of the Board of Regents. Possibly the room may be left as is until the next meeting of the Board of Regents, at which time decision may be made concerning its furnishings.

PRESIDENT MORGAN: Anyone who has had anything to do with building recently will certainly be impressed with the fact that our Committee has stayed within the budget, with the exception of \$153.88. It will require action by the Regents relative to this deficit.

. . . On motion by Dr. David P. Barr, seconded by Dr. Reginald Fitz, and unanimously carried, the Board of Regents appropriated \$153.88 to cover this deficit. . .

PRESIDENT MORGAN: This is the end of the agenda for the Regents' meeting and the Chair relinquishes his position to Dr. Walter L. Palmer, Chairman of the Board of Governors.

. . . Dr. Walter L. Palmer, Chairman, assumed the Chair, and called to order the meeting of the Board of Governors.

CHAIRMAN WALTER L. PALMER: Dr. Morgan, we thank you and the Board of Regents for your great courtesy in inviting the Governors to meet with the Board of Regents today. We shall, first, have the reading of abstracted Minutes of the last meetings of this Board.

. . . The Secretary, Mr. E. R. Loveland, read an abstract of the Minutes of the three meetings of the Board of Governors held during the 1947 Annual Session. There were no corrections, and the Minutes were accepted as read. . .

CHAIRMAN PALMER: We shall proceed to the receipt of reports from Committees. The first will be from the Governors' Committee of Five on proposals concerning methods of elections of Officers, Regents and Governors, Dr. Edgar V. Allen, Chairman.

DR. FRANK J. HECK (ALTERNATE for Dr. Allen): Dr. Allen is ill and has been away for a number of weeks. Unless Dr. Wolverton, another member of the Committee, has some definite information, I know nothing about the report of this Committee.

DR. BENJAMIN F. WOLVERTON: Dr. Allen, as Chairman of this Committee, sent out a questionnaire to all the Governors last winter. However, I have heard nothing from Dr. Allen since that time, and I would suggest a delay in the report from this Committee until our next meeting.

CHAIRMAN PALMER: We shall consider this a report of progress, and defer it until a future meeting.

The next Committee report is that of the Advisory Committee on Postgraduate Courses, Dr. Edward L. Bortz, Chairman.

DR. EDWARD L. BORTZ: Mr. Chairman, our current spring schedule of courses is operating as follows:

Course No. 1—MEDICAL ASPECTS OF RADIOACTIVITY

U. S. Naval Medical School

Bethesda, Md.

February 18-27, 1948—

has been concluded, with a registration of 22 from the College, augmented by a considerable number of Naval and Military Officers. The course was received with enthusiasm. In view of the importance of the new and rapidly expanding

field of atomic energy and its bearing on medical science, this Committee this morning expressed the opinion that the College should stress the importance of members taking every opportunity to inform themselves concerning this rapidly expanding field. The Committee recommends that from time to time editorials be presented in the *ANNALS OF INTERNAL MEDICINE*, written by such authorities as Dr. Stafford L. Warren, and other men in the forefront of this field, in order that our members shall keep abreast of developments. Furthermore, the Committee is of the opinion, and desires to recommend, that for the various courses of the College, where possible, there be invited to the faculty an authority in the field of atomic energy, as it applies to particular specialties.

The Committee desires to recommend that contacts be established with those schools and centers of graduate training, such as several of the medical schools, the group in Chicago, and the appropriate departments of the Army and Navy, in order to enlarge the opportunities for College members to take advantage of this instruction. Also, the Committee recommends for your consideration, that the various Regional Meetings which you Governors organize include on the program something in the field of atomic energy. Such an outstanding authority as Dr. Shields Warren has made a statement that this (atomic energy) is the most important and significant development in medical science since the discovery and the development of the microscope. In view of the unsettled state of affairs of the nation and the possibility of future involvement, the medical profession certainly, and surely the authorities and leaders of organized medicine, are obligated to know about the potentialities, the dangers that are inherent in the possible use of atomic bombs. Whether or not it would be utilized in a national emergency, or whether or not a catastrophe should occur in other ways, the medical profession should know its responsibility. I am sorry to say that from my contacts and from my travels throughout the land, I confidently believe that our medical profession is very inadequately informed about the dangers inherent in atomic energy and the handling of radioactive isotopes. That is one phase.

Another phase, and even more important, concerns the researches going on. Your Committee is of the opinion that every possible channel for instruction of the membership of the College should be developed and encouraged to facilitate better understanding of the basic principles and the details inherent in both radioactive and stable isotopes.

About two years ago the College was the first organization, I believe, to offer a course in radioactive isotopes. A small group of possibly ten or twelve men came to the Research Department of the Lankenau Hospital in Philadelphia to study, and all of them stated that their work there was highly beneficial, and they hoped the course would be repeated. With that in mind, we pursued the possibility of having our members attend courses given by the Navy Department in Washington and accomplished that end. We believe in the future we shall be able to continue to send men to special courses given by the Army and Navy, by the University of Chicago and other institutions.

#### Course No. 2—PHYSICAL MEDICINE FOR THE INTERNIST

Mayo Clinic and Mayo Foundation for Medical Education and Research

Rochester, Minn.

March 22-26, 1948—

Dr. Frank H. Krusen, F.A.C.P., Director; registration 17, supplemented by a number of local physicians.

## Course No. 3—CARDIOVASCULAR DISEASES

University of Southern California School of Medicine  
Los Angeles, Calif.  
April 12-17, 1948—

Dr. George C. Griffith, F.A.C.P., Director; registration 47; a very popular course.

## Course No. 4—ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION

Massachusetts General Hospital  
Boston, Mass.  
May 10-15, 1948—

Dr. Conger Williams, Director; registration limited to 26.

## Course No. 5—INTERNAL MEDICINE

Gallinger Municipal Hospital  
Washington, D. C.  
May 17-22, 1948—

Dr. Wallace M. Yater, F.A.C.P., Director; present registration 74; capacity 100.

## Course No. 6—CLINICAL ALLERGY

Roosevelt Hospital  
New York, N. Y.  
May 17-28, 1948—

Dr. Robert A. Cooke, F.A.C.P., Director; registration limited to 8.

## Course No. 7—CLINICAL NEUROLOGY

Jefferson Medical College of Philadelphia  
Philadelphia, Pa.  
May 24-29, 1948—

Dr. Bernard J. Alpers, F.A.C.P., Director; present registration 38; capacity 75.

## Course No. 8—PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE

University of Illinois College of Medicine  
Chicago, Ill.  
May 31-June 5, 1948—

Dr. A. C. Ivy, F.A.C.P., Director; current registration 180; capacity 200. With such a large registration, this course becomes more of a convention than a graduate course. This is unfortunate, because the objective of our courses should be for the student-physician to come into close intimate contact with the teacher. This is the second time we have given this course, the first one being given with sensational success under Dr. Julius H. Comroe, Jr., of Philadelphia. We believe interest in the basic fundamentals on which medicine is practiced has been stimulated in a very generous measure by the insistence of the American Board of Internal Medicine that men be well grounded in the basic sciences.

## Course No. 9—DIABETES AND GENERAL MEDICINE

New England Deaconess Hospital  
Boston, Mass.  
July 12-16, 1948—

Dr. Elliott P. Joslin, F.A.C.P., Director; current registration 35; capacity 75. This is our first experience in arranging summer courses, and it is probable that this course will be filled to capacity.

Now reporting on the 1948 schedule of courses already approved by the Board of Regents, but subject to some alteration, we propose the following:

. . . (Dr. Bortz outlined the proposed courses for the autumn of 1948 in considerable detail, but inasmuch as this Roster of courses has been published elsewhere in this journal, it is not repeated here.) . . .

There are other courses under consideration. I want to say something about psychosomatic medicine. A very successful one-week course was given a year or so ago by Dr. Franklin Ebaugh, and the Committee has waived the advisability of another course. We are of the opinion that to split off one particular small specialty in a larger, important field is probably not in the tradition of our program. We are looking forward, not this year, but perhaps next year, to give a course in psychiatry, with the consideration of psychosomatic medicine as it fits into that field.

Then in 1949 we are keeping in mind enlarging the opportunities for more instruction in the Physiological Basis for Internal Medicine and the Mechanics of Disease. We shall have courses in hematology, cardiology and other fields, and if the Governors have any suggestions or comments, the Committee will be grateful for them.

. . . On motion by Dr. William D. Stroud, seconded by Dr. M. D. Levy, the report of the Committee was accepted. . . .

CHAIRMAN PALMER: The next on our agenda is a report from the Executive Secretary on Regional Meetings.

. . . Mr. E. R. Loveland, Executive Secretary, distributed a duplicated outline of all Regional Meetings held during 1947 and to date in 1948, or scheduled later in 1948. . . .

CHAIRMAN PALMER: The Governors will recall that at the last meeting of the Board there was considerable discussion of the relative merits of large multi-State Regional Meetings, as contrasted with the small single State Regional Meeting, and I think it was concluded that these two types of meetings each have their special merits and advantages, as well as disadvantages. It was mutually agreed to leave the decision to the men in each territory to decide which type of meeting they prefer.

The only remaining item on the agenda for this session is a group of announcements, which will be made by the Secretary at the end of the meeting. I wish now to turn the meeting back to President Morgan.

. . . President Morgan resumed the Chair. . . .

PRESIDENT MORGAN: The Committee on Credentials has a matter which they would like to bring to the attention of this combined meeting, and I shall ask Dr. George Morris Piersol to take the floor.

DR. PIERSOL: These matters are only in the form of suggestions, and there are a great many arguments pro and con that may be advanced. These suggestions are presented by the Credentials Committee for discussion, not with the object of lightening their own troubles and burdens in passing upon candidates. However, because of the feeling of inadequacy which they experience continually, and because of difficulty in arriving at accurate and definite conclusions in regard to the qualifications of certain candidates, these suggestions have been prepared. It was suggested from time to time, over a number of years, by various members of the Credentials Committee that it might be best to exclude from the College those who, although closely affiliated with internal medicine, are not primarily internists, such as neuropsychiatrists, dermatologists, or some other affiliated specialists whose fields are set forth in our informative booklet. Heretofore, we have always taken them. Their number grows, not excessively, but steadily, and with this increment, the size of the College, likewise, grows steadily.

It has been assumed that the College is not interested in becoming an enormous group, but rather to make it an adequate, compact and representative body of those represented in internal medicine.

In order to bring this or any other change about, it is going to be necessary to amend the By-Laws. It is a cumbersome and important matter that must be carefully



considered. The suggestion is to eliminate at some specified future time from admission to membership those groups who, though affiliated with medicine rather than surgery, are not primarily internists. This could be done without subjecting them to any serious inconvenience. They all have their own extremely efficiently functioning certifying boards and special societies in which they are very much interested. The groups particularly in mind are the radiologists, dermatologists, syphilologists, neuro-psychiatrists, those in industrial medicine, and possibly pediatricians.

The second suggestion from the Credentials Committee is equally important and already has been a source of much discussion over the years. You will recall that less than five years ago it was suggested, brought up, discussed and voted down that one of the qualifications for admission to Associateship should be certification by the appropriate specialty board. This involves a principle which is quite basic, and there are those who believe in it heartily, and there are those who are equally vehemently opposed. It is my recollection that the Board of Governors previously did not look with favor upon such a change.

In order to meet the issues to some extent at least, a Survey Committee was appointed, under Dr. William S. Middleton, Chairman, which Committee brought in a very thoughtful and careful report. Their recommendations have been approved and have been incorporated in our By-Laws. The Credentials Committee is now doing its best to operate under those regulations. However, any of these regulations are subject to great variability and, as good as they are, constitute different yardsticks for application. It was, therefore, actually brought up by and instigated by, not only those who in the beginning advocated certification as a prerequisite for Associateship, but those previously vehemently opposed to the proposal, who, having watched over a period of years the uncertain workings, finally came to the conclusion that it is very difficult for a small Committee, or even for the Governors, to try to pass upon the eligibility of an individual. That involves the opinions of a good many people and variabilities are not controllable. If it were flatly stated, "if you are an internist, demonstrate the fact that you are a bona fide internist, both with intention and in your ability and in your professional attainment by appearing before the board and being certified," then there is no further necessity of exploring all sorts of collateral evidence to establish that the candidate is an internist, or ever going to be an internist.

It is only fair in discussing this matter to say that so thoughtful a person as Dr. Ernest E. Irons, who was unable to be here because he is absent from the country, wrote the following letter to the Executive Secretary, which was handed to the Credentials Committee at this meeting:

"(1) As I take it the purpose of the College is primarily the promotion of standards and education in the field of internal medicine. There are other considerations of fellowship, acquaintance and the stimulation of younger men by prospective membership which are, along with others, highly desirable.

There has been what seems to me an unfortunate creation of divisions of internal medicine which have developed with the rapid increase in special knowledge. Such divisions are unavoidable and indeed are desirable and necessary. However, these divisions into sub-specialties need not be carried into the question of standards of accomplishment in internal medicine. It is true that gastro-enterology is on perhaps a little different basis than radiology since radiology partakes in its interest both of medicine and surgery. I believe that the inclusion of the several groups such as pediatrics, neurology, psychiatry, pathology, etc., is really of great advantage to the College in broadening the viewpoint of the members.

"(2) The argument that the College is getting too large seems unfortunate, because as it is to be of maximum value to medicine, it should not become

a private group. If the membership is limited with a constantly expanding number of persons who are qualified for membership and still cannot enter, the situation is set up whereby other organizations will come into the field and we will create our own competition.

I am aware that carrying out the above policies will not solve the mechanical questions and labor of the Credentials Committee. This Committee has done marvelous service and is doing it, but I doubt the wisdom of changing the policy of the College in order to lighten the work of the Credentials Committee."

That, Mr. President, is the gist of the situation.

PRESIDENT MORGAN: You have heard these suggestions. Unless it is the will of the group that we take positive action on these two important questions, and they certainly are important, I would suggest that we here and now discuss these matters for thirty minutes and take no action until the next meetings of the Regents and Governors.

Of the two questions raised, I might say one really decides the other. If we should decide that certification shall be specifically by the American Board of Internal Medicine as a prerequisite for Associateship, the question of any candidates coming in from dermatology, neuropsychiatry, radiology, etc., will be automatically settled. If there are neurologists, for instance, who want to be internists as well and will come up before the Board of Internal Medicine, they would qualify insofar as that requirement is concerned.

DR. JAMES E. PAULLIN: Doesn't the report of the Survey Committee under Dr. Middleton last year settle this matter, insofar as the By-Laws are concerned?

DR. MIDDLETON: Only insofar as making certification necessary for Fellowship, not for Associateship, nor do the By-Laws specify the particular specialty board. Dr. Piersol's suggestion would limit this to the American Board of Internal Medicine, and would apply the rule to Associates as well as Fellows.

DR. LAWRENCE PARSONS: I have been a member of the Board of Governors for a few years, and I am one of those funny doctors, a pathologist, and have gotten a great deal of benefit from them. As long as there is nobody to speak for some of us, I should like to say a word or two in our behalf. It has been a pleasure for me to come here, and I have felt very proud, in a certain sense, to be associated with such a fine group of physicians. I always felt that a man who had "F.A.C.P." after his name held a certain amount of distinction. I am sure that is the general opinion of medical men. I hope that some of the specialties in medicine which are very intimately associated with internal medicine, such as pathology, will not be taken out of this organization.

It certainly has been most helpful to me to be associated with the College, and I hope that I will be allowed to remain. I should certainly like to see that clinical pathology of all things is not taken away from internal medicine. Anyone who reads the journals sees some of the finest contributions to clinical pathology from professors of medicine. Dr. Cecil Watson, for instance, has written many fine articles that have appeared in the American Journal of Clinical Pathology. On the other hand, clinical pathologists have published articles in the ANNALS OF INTERNAL MEDICINE and in the Archives of Internal Medicine.

PRESIDENT MORGAN: Thank you, Dr. Parsons. I am sure we feel the same about clinical pathologists.

DR. WILLIAM S. McCANN: I think there is much wisdom in Dr. Irons' letter. We should not forget that the creation of the specialty boards has always created some special colleges. There would be a great disadvantage to American medicine if the general body of physicians, as distinguished from surgeons, were to be weakened by any more division. I think the College should keep its place as the representative

of the non-surgical part of the profession. It would be a grave mistake, in my opinion, to exclude any but certified internists from this body. I believe that the matter of certification will take care of itself in the future.

At the present time there are undoubtedly many able men who have established themselves well in their field of internal medicine, and who would be reluctant to tackle the present type of written examination by the boards. It would be too restrictive if we were to insist upon certification for admission to Associateship.

DR. PIERSOL: There still exists confusion of understanding. At the present time it is perfectly clear an Associate does not have to be certified. A candidate can come up for Associateship if he is an internist, or follows any of the subdivisions of internal medicine, or any of the affiliated branches of medicine. That is all, as it stands today. The new question is shall we continue to take in candidates who are following these affiliated subjects in medicine. We should make it clear that pathologists, biochemists, and all those engaged in the basic sciences should be included. I think the present problem mostly concerns the continued admission of dermatologists, syphilologists and radiologists, who are in very border-line specialties when it comes to internal medicine. At present no one has to be certified, unless he aspires to be a Fellow; and, if he is a neurologist, he must be certified by the American Board of Neurology and Psychiatry; if a dermatologist, by the American Board of Dermatology and Syphilology, and so on. There has never been the thought that if a man followed an allied specialty, such as neuropsychiatry or dermatology, he should be forced to take an examination by the American Board of Internal Medicine.

The present idea is to exclude from membership in the future, not making it retroactive, those who are not internists, but who practice some of the clinical specialties. It has nothing to do with the subspecialties of medicine. Then if we were to say we would take in only internists, regardless of their subspecialties, in order to clarify who is such a person and to have criteria that are accurate and workable, we would say that he ought to be certified by the American Board of Internal Medicine, "or his respective board," which would still have to be put in, because certainly no one would try to exclude the basic sciences, which form many foundations of internal medicine.

DR. WALLACE M. YATER: It might clarify the situation just a little to remind the members here that we cannot accept as Associates men who do not have the prerequisites, in our opinion, to be admitted to the board examinations. That is where the difficulty arises. The Credentials Committee is not in a position to decide, in many cases, whether a man has the prerequisites that the Board will require. It would be so much easier if the candidate had already taken his board examinations, because we would then have that information all settled. In other words, we think he should have his basic requirements before we can accept him as an Associate.

DR. E. DICE LINEBERRY: May I ask what the percentage is of the members in the allied specialty groups?

MR. LOVELAND: I cannot tell you specifically without checking the Membership Roster. There has been a steady increase in the number of candidates from some of the allied specialties, such as neurology and psychiatry. I would guess that we have among our members about three hundred neuropsychiatrists. There has been a definite decline in the number of pediatricians seeking membership. I think we have less than one hundred and fifty among our members. We haven't more than one hundred in the field of radiology. I should think we have no more than thirty or forty dermatologists, and very few physiologists.

DR. ALEX. M. BURGESS: We should be clear on anything we do on this subject. We are dealing with two separate topics—the question of elimination of certain allied fields of work, and the question of requiring certification as a prerequisite for Associateship. If we think back a little and realize the history of the College and its development throughout the years, we shall note that it has changed a great deal. The

efforts of the Board of Governors over a period of years have tended to bring in more distinguished men and keep out the less distinguished, and Associateship or Fellowship now represents a much greater distinction than it did twenty years ago. Now this College has created the American Board of Internal Medicine with its requirement for certification, which, as I see it, has come into direct conflict with Associateship. The members of the Credentials Committee are feeling that conflict, and it is up to us to clear the matter; if, as we now hope, the Board of Internal Medicine is able to investigate, properly screen out and certify all competent internists, it then seems to me that Associateship, as well as Fellowship, should be a step higher and a step further along in the career of a physician. That should be the ideal we strive for in the future. If that is carried out, it simplifies very greatly the practically impossible task to which the College is committed through its Credentials Committee, namely, the election of these men. I do not infer that the American Board of Internal Medicine can ideally select these men, but it is an agency for that purpose, and it is trying hard to do so. If certification becomes a prerequisite for Associateship, then the Committee on Credentials is freed from the conflicts, including determination of the candidate's real specialty, the follow-up on certification between Associateship and Fellowship, the careful checking of time limits, and so forth. It would simplify and greatly improve the situation, and would put the College on a level of greater distinction, increasing the value of the College to all concerned.

DR. TURNER Z. CASON: I am opposed to the sentiment just expressed. Does not the premise of the College indicate its purpose to be the extension of medical knowledge and the improvement of medicine? If we do what has been suggested, we shall be getting away to a certain extent from this very thing. A young fellow comes along, qualifies for Associateship and must immediately begin to work on preparation for his boards. We encourage him; we offer him graduate courses; we make reduced rates, and so forth. If we say he cannot become an Associate until he has passed the board, we are not helping him to do the very thing that we started out to do. I have another thought. In some communities the board is valued at more than the College—at least it is in some of the hospitals, and if we start excluding them that way, I am afraid they will pass the board and pay no further attention to the College. That is a phase worth considering. I think our plan has worked out best the way it stands now.

DR. BURGESS: I would like to answer just one point; perhaps that is the crucial issue, and Dr. Cason may be more right than I, but I should like to point out the following: a young man becomes an Associate, he has three years before he is eligible to become a Fellow, but he may be prevented, so easily by illness or something else, from taking the board examinations for say three years, and then if he fails the first time, he has a year left; if he fails the second time he cannot retake the examination for two years; his Associateship will have lapsed, and he will have been dropped from the College Roster. It seems to me if we keep our present plan, in all fairness to these candidates, they must have a longer period of Associateship, in order to qualify for Fellowship, in the now restricted five-year period.

DR. MAURICE C. PINCOFFS: I wonder, if the Credentials Committee had the standard of certification before election to Associateship, if it would not find some difficulty in setting up adequate criteria for advancement to Fellowship. Is it not very helpful, under our present plan, to have this certification constitute one of the important criteria for Fellowship? Other and new criteria, it would seem to me, would put an added load on the Credentials Committee. I would like to find out what the Committee has in mind as specific criteria for passage from Associateship to Fellowship.

DR. PIERSOL: The general principles are set forth in the regulations that were adopted following the Survey Committee's report. If you will read that over, you will get a good idea. I might say in passing that there is a steadily increasing number of proposals for Associateship from men who have already been certified. It is astonishing how that number has risen.

Now, certification is not synonymous with being elected a Fellow. If a man is certified, an internist, and otherwise qualified, in order to be advanced to Fellowship he must do one of several things: he must have shown adequate interest in furthering his medical career; he must have acquired some sort of hospital or teaching affiliation; and he must have contributed in some creditable manner to the literature. There are many candidates turned down who are certified, but who have never written or done anything of any note, and have not grown medically during their five years of Associateship. I do not suggest that the College should set up standards comparable to some of the very elite scientific groups, where a man must have demonstrated his ability to do original research or outstanding work of some other character before he is admitted, but in the College he must have shown some aptitude, some energy and some interest as expressed by the professional attainment in teaching or hospital appointment, or other public medical activity. He must have contributed, not merely a manuscript largely gathered from the textbooks of medicine and read at a staff meeting, but he must have really contributed something which a critical Editor would be willing to publish.

DR. JOSEPH D. MCCARTHY: I am of the impression that an Associateship in this College is a probationary period. Am I correct?

PRESIDENT MORGAN: Yes.

DR. MCCARTHY: I am thinking of the candidate who qualifies to take his board examinations. He becomes an Associate; he proceeds to attain certification. In the future some of these younger men will not be able to qualify as rapidly for certification, perhaps, as they have been the past few years. I quite agree that the Associate term should be a spur to that man, for him to know that he must go ahead and attain certification before he can become a Fellow.

DR. CHARLES F. TENNEY: I think it would be interesting to hear what percentage have already been certified before being proposed for Associateship this past year.

DR. PIERSOL: Approximately 75%.

PRESIDENT MORGAN: I wonder what the Canadian's experience has been. What about the Royal College in Canada and its attitude, Dr. Moffatt?

DR. CHARLES F. MOFFATT: Conditions up North are different from what they are here. We have one College, the Royal College of Physicians of Canada, to which there is one examination. There is no preliminary examination, although there is one minor part, and then the final examination, which admits to "F.R.C.P." We have no probationship. In comparing these examinations, we believe they are about on par with those of the American Board of Internal Medicine. The examination is the only requirement, apart from the usual rule of showing a certain number of papers and an aptitude for internal medicine, which follow very much the same rules as the American College. There are certain degrees which we accept in Canada, such as "F.R.C.P. of London," "F.R.C.P. of Edinburgh," and occasionally "F.R.C.P. of Ireland." It is not the intention to tighten the restrictions at the present time.

DR. LINEBERRY: How many candidates fail because of failure to attain certification, rather than for any other reasons?

DR. PIERSOL: Not too many, possibly less than 5%.

DR. LINEBERRY: If we wish to reduce the membership we could raise the age limit and do the same thing.

DR. PIERSOL: I may say that there have been two suggestions put forth—one that the age limit for Associateship be increased to 35, and another that the Associate term be extended for more than five years.

PRESIDENT MORGAN: Our time has expired, and, Dr. Palmer, with your permission, I will declare the meeting adjourned.

... The meeting adjourned at 5:15 p.m. ...

Attest: E. R. LOVELAND,  
Executive Secretary

## ABRIDGED MINUTES OF THE BOARD OF REGENTS

SAN FRANCISCO, CALIF.

APRIL 20, 1948

The second meeting of the Board of Regents, held during the 29th Annual Session at San Francisco, Calif., was called to order at 1:15 p.m. in Room 203 of the Civic Auditorium on April 20, 1948, with President Hugh J. Morgan presiding, and Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Hugh J. Morgan, *President*; Walter W. Palmer, *President-Elect*; Reginald Fitz, *First Vice President*; Francis G. Blake, *Second Vice President*; Charles T. Stone, *Third Vice President*; William D. Stroud, *Treasurer*; George Morris Piersol, *Secretary-General*; Walter B. Martin, William S. Middleton, James E. Paullin, LeRoy H. Sloan, George F. Strong, William S. McCann, T. Grier Miller, Charles F. Moffatt, Charles F. Tenney, David P. Barr, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Maurice C. Pincoffs, *Editor, ANNALS OF INTERNAL MEDICINE*; Walter L. Palmer, *Chairman, Board of Governors*.

The Secretary was ready to present a full transcript of the Minutes of the preceding meeting, but by resolution, seconded and duly carried, that was dispensed with. Among communications presented to the Board were the following:

- (1) A letter from Dr. Ernest E. Irons, reporting that he had attended two sessions of the Emergency Medical Service Committee on behalf of the College, and discussing the proceedings of the meeting. Several types of laws to be presented to Congress, concerning conscription, were discussed, but at that time it had not been possible for the doctors to present a firm statement, because they had not seen the proposed draft of the law. The discussion had hinged about the proposal to provide in the draft law for men up to 26 years of age, but to require a draft of physicians up to 45 years of age. The Committee on Emergency Medical Service had opposed this as being discriminatory and reflecting on the patriotism of the doctors.

... The discussion of this subject by the Regents was by direction omitted from the Minutes. ...

- (2) A letter from Dr. Noble Wiley Jones, regarding Honorary Fellowships. Dr. Jones submitted a communication to President Morgan advocating the establishment of honorary memberships or fellowships in the American College of Physicians, to honor distinguished men here at home or abroad, pointing out that the Royal Australasian College of Physicians had conferred Honorary Fellowships on two Fellows of the American College of Physicians, whereas the American College of Physicians has no machinery by which such compliments may either be returned or initiated.

President Morgan proposed that the matter be referred to the Committee on Constitution and By-Laws "for their consideration as to whether or not the College should create Honorary Fellowships, and, if so, provide the necessary amendments to the Constitution and By-Laws."

- (3) A letter from Dr. Albert M. Snell, Rochester, Minn., concerning the stimulation of interest in the creation of an international society of internal medicine. Dr. Snell and Dr. David P. Barr had been invited to attend an organization meeting, and the sponsors of the movement had asked that the

American College of Physicians, the Association of American Physicians and the Society for Clinical Investigation be contacted and their interest solicited. Dr. Barr stated that he had been invited to attend and had replied that such an organization might find a useful function, but that he would be unable to take part in its organization. Dr. Barr expressed the opinion that perhaps this is an inappropriate time to undertake this venture.

President Morgan asked for general discussion.

DR. JAMES E. PAULLIN: Mr. Chairman, in view of the fact that we are organizing a World Medical Association, I move that this communication be referred to the Committee on Public Relations, and that they report back at the next meeting of the Board of Regents.

... The motion was seconded and regularly carried. . . .

- (4) An announcement from Dr. Walter W. Palmer of the appointment of Dr. Walter L. Palmer, Chicago, as official representative of the College at the Conference on Nomenclature of Disease, meeting at the Headquarters of the American Medical Association on June 23, for the purpose of setting up committees and carrying out the necessary preliminary work toward the revision of the Standard Nomenclature of Disease and for its publication early in 1950.
- (5) A letter from Dr. Lowell A. Erf, Chairman of the Scientific Exhibit Committee of the Centennial Celebration meeting of the Medical Society of the State of Pennsylvania, inquiring if the American College of Physicians would be interested in presenting an historical exhibit.

It was the sense of the meeting that the Secretary be requested to reply, stating the College is not in a position to provide an exhibit for this occasion.

- (6) MR. E. R. LOVELAND: There were two communications in a manner related to one another—one was submitted through the College Governor for the Veterans Administration, pointing out that in many instances the regulations of the College preclude Veterans Administration physicians from qualifying for Fellowship in the College, for the simple reason that certification is a prerequisite, as well as membership in one's recognized state and national societies, including the American Medical Association. On the other hand, in certain localities, the American Board of Internal Medicine will not admit a physician to its examinations unless he is a member of the American Medical Association, and there are in some locations such regulations that a Veterans Administration physician may not join the local county and state medical societies, and thus is not eligible for membership in the American Medical Association. This matter has been placed before Dr. George F. Lull, General Secretary of the American Medical Association, and he has assured us that in June this situation may be remedied, extending to Veterans Administration doctors the same courtesies that at present are extended to Army and Navy physicians, allowing them to become members of the American Medical Association without necessarily membership in county and state medical societies.

The other communication originated from the College Governor for Panama and the Canal Zone, in which he points out that there is practically nothing that he can do, as Governor, toward presenting candidates for membership in the College from that area. Physicians in Panama and neighboring countries, and it is also true of Cuba or Mexico, or any other Central American country, are not eligible for admission to the examinations of the American Board of Internal Medicine, or any other certifying board, and, thus, could not comply with the certification requirement for advancement to

Fellowship in the College. That is, physicians not eligible for membership in the American Medical Association, therefore, cannot be admitted to the American Board examinations, and, therefore, under present regulations could never qualify for Fellowship in the College, yet it is our published regulation that a citizen physician of any North American country is eligible for College membership. The result of this situation is that physicians outside of the United States or Canada can only enter the College at present through direct Fellowship.

DR. MORGAN: Dr. McCann, will you speak on this from the point of view as Chairman of the American Board of Internal Medicine?

DR. WILLIAM S. MCCANN: This matter has been discussed in our meeting, and my recollection is that the feeling of the Board is that the requirements for admission to the examinations should be modified, in order to permit Veterans Administration doctors to come in. I do not remember hearing about any discussion of citizens from other countries, such as Panama, Cuba or Mexico.

DR. MORGAN: In order to bring this matter into complete focus from the point of view of the springboard from which the American Board approached it, I make this comment: in a certain state it costs \$125.00 or \$150.00 dues in the county medical society, and the American Board questions seriously if it had the right to insist that some young doctor in a Veterans Hospital, or any other activity, who wanted to be examined and was eligible from other standpoints, that he expend such a sum for county society membership before admission to the examinations. That was one practical feature of the matter. We consider this to be a very serious question.

DR. PAULLIN: I move that this communication be referred to the Committee on Public Relations for study, and that they report some recommendation at the next meeting of the Board of Regents. This is important, and we ought to study it.

. . . The resolution was seconded and regularly carried. . . .

(Communications continued):

- (7) From Dr. Hugh J. Morgan concerning interpretation of regulations governing the Bruce Award.

DR. MORGAN: After consulting the Minutes of previous meetings, I recommend the following interpretation, subject to confirmation by the Board:

(1) Under ordinary circumstances traveling expenses of the recipient will be less than \$125.00, in which case he shall receive a stipend of \$125.00;

(2) In any case where the traveling expenses (such as in 1948 at San Francisco) exceed \$125.00, there shall be no stipend to the recipient, but his traveling expenses, according to the normal allowances made, shall be paid in full by the College, the additional amount beyond \$125.00 to be taken from the general funds of the College.

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. George F. Strong, the recommendations were unanimously approved. . . .

- (8) From Dr. Hugh J. Morgan concerning traveling expenses of Governors to the Annual Sessions.

MR. LOVELAND: Dr. Morgan asked my office to analyze the cost, under varying circumstances, of paying to the Governors an allowance for travel to the Annual Sessions, similar to that paid to the Board of Regents; that is, the round trip train and pullman fares. Such an analysis has been made, and it shows that for Annual Sessions held in the east, middle west and far west, with Philadelphia, Chicago and San Francisco selected as typical cities, the cost at present would be as follows: Philadelphia, \$7,472.00; Chicago, \$6,454.00; San Francisco, \$12,410.00.



DR. MORGAN: The idea that it would be well to explore this matter stemmed from agitation that grew out of the Board of Governors' meetings last year, relative of the importance of the Governors to the College, and the feeling on the part of a few that the Governors were really somewhat sidetracked and by-passed. It is extremely important that Governors be present for the Annual Meetings, but it is quite essential that the Regents, constituting the board of directors for the transaction of official management of the College, be present. The Governors are the field representatives of the College, the ones who more than any one else determine the quality of the membership, because they feed into the Credentials Committee the information which makes it possible for that Committee to act wisely on candidates. The Regents may favor in principle the handling of the matter of expenses of the Governors on the same basis as for the Regents. . . .

. . . There was general discussion headed by Dr. Alex. M. Burgess, Dr. Maurice C. Pincoffs, Dr. Charles F. Tenney, and others, favoring this action, if it is possible financially. On a motion by Dr. Burgess, seconded by Dr. Paullin, and carried, it was

RESOLVED, that the matter be referred to the Committee on Finance to study the feasibility of the plan, and to report back to the Regents.

- (9) From Dr. Arthur J. Patek, F.A.C.P., relative to the matter of rebating of fees from laboratories.

DR. MORGAN: Dr. Patek wrote to the College relative to the matter of rebating of fees from laboratories, x-ray laboratories, clinical laboratories, and so forth, a matter about which we have been hearing so much in the newspapers recently. I would like the College to take official action which would lead to the withdrawal of the approval of hospital appointments of men who are known to accept such rebates. I wrote him unofficially that the matter would be brought to the attention of the Board of Regents, but pointed out that this College is not an operational organization in that sense, and that it is unlikely that our Board would take any formal action; that the Constitution and By-Laws of the College and Fellowship Pledge preclude acceptance by members of rebates, or fee splitting practices. Dr. Patek is much exercised about this matter and wrote a fine letter to the American Medical Association a few weeks ago, and he wants to do something about it.

MR. LOVELAND: Mr. President, there is a similar matter before the Committee on Public Relations at the present time.

DR. MORGAN: We can ask that this communication be answered by the Committee on Public Relations on the basis of their other recommendations, and we refer the matter, therefore, to that Committee.

May we now have a report from the American Board of Internal Medicine, Dr. William S. McCann, Chairman.

DR. MCCANN: Dr. Morgan and Gentlemen: At the last meeting of the Board of Regents we discussed the mechanism for the approval of hospitals for training. The question was raised of a joint action of some sort which would aid the Council on Medical Education and Hospitals in performing its task of survey and approval. A Liaison Committee was appointed, consisting of Dr. Reginald Fitz and Dr. LeRoy H. Sloan. The difficulty of the Council appears to be that of getting sufficient personnel to make the inspections, rather than the lack of funds. At our last meeting it was suggested that a panel of part-time inspectors be made available to the Council, and that these men be paid \$50.00 per diem and expenses, according to the formula used in the Veterans Administration for their consultants and section chiefs. The method of selection for such a panel was not fully discussed. It was felt that inspectors could be, or should be, Fellows of the American College of Physicians and Diplomates of the American Board of Internal Medicine. How this panel should be drawn was left unsettled. Dr. Fitz may comment on this later.

Now we might say a word about the result of the American Board examinations. I believe that the Board is utterly convinced now that the present type of examination, the so-called written portion, is better than the old essay type, that it is more fair and more searching. Each new examination, as it has come along, has been set so as to eliminate flaws found in the previous ones. I believe about the same percentage of people pass this form of written examination as passed the old essay type.

With regard to the oral examination, our Board was better satisfied with the oral examination just held here in San Francisco than with any oral examination which I have attended in the seven years of my association with the Board. Curiously enough, a slightly greater number of men failed in this oral examination than was customary in previous examinations. Usually the rate of failures is between 25 and 30 per cent. It is estimated that about 40 per cent failed the current one.

Now, I believe this was a good examination. The place where it was held was extraordinarily well adapted to the purpose; that is, material was excellent, well studied and the records were fine. The moot questions coming up could be settled from the dates in the charts, and I think we had an unusually good chance to evaluate the candidates.

What are the implications of this? It shows that there is a considerable number of men who can pass a very difficult written examination, but may be quite inadequate at the bedside. The converse may also be true, that there may be some excellent doctors, clinicians and internists who would not do so well in a written examination. We ought to ask ourselves searchingly whether we are excluding some very desirable people by the very stiff written examination. I think we have to admit that a certain number of men fail because of nervousness. All of our examiners have encountered men with whose performance they were familiar, but who went to pieces under the strain of examination. By and large, I think the men who fail do so because they have been trained in institutions which lack the type of discipline that produces the really sharp internist.

That leads me to the next step in the procedure. The Board has considered that we should at this time tabulate our experience in the whole history of the Board, in order to determine what hospitals and training agencies had given up a large number of failures. I believe an arrangement will be made to carry out this study, and when we get this information, it could be utilized by the Council on Medical Education and Hospitals and by the Board in determining the question of future approval of institutions for training. The hospitals themselves, if they were aware of this fact, could take corrective measures. Perhaps all that one would need to do would be to publish the results in the American Medical Association's Journal, such as is done for the state board examinations, so that one can tell what percentage of graduates of a school fail in those examinations.

There is still under discussion the matter of holding small regional oral examinations in different parts of the country by only a part of the Board. That is, taking the members of the Board who reside in the region and holding the examinations on a smaller scale. That would permit us to utilize many excellent hospitals which are not big enough to accommodate the larger numbers, such as at our present examinations. That plan has many advantages and many disadvantages, which have led the Board to withhold their final decision.

It may be unnecessary to adopt this measure to deal with the backlog of unexamined candidates if we can repeat the oral examinations in the future as successfully as we have done here in San Francisco. The Board is very grateful to the local men who have provided us with such splendid facilities.

I shall be retiring from the Board as of June 30 of this year, after several years of service. I should like to pay a tribute to my colleagues on the Board. I have never seen a group of men who worked more wholeheartedly and more devotedly for the

cause of improving the training of internists and the practice of medicine. Never have I seen any evidence of any desire to restrict the number of men certified. The effort has been solely to improve the method of determining what the qualifications were. Our methods are admittedly somewhat imperfect, but I think that they have been steadily improving, and I have no doubt that further improvement will continue.

PRESIDENT MORGAN: Thank you, Dr. McCann, for a most interesting and fine report as the retiring Chairman of the American Board of Internal Medicine. It is only fair for me, one member of that Board, to say that much of the progress with relation to the technique of doing the job, which the Board feels constitutes a great responsibility, has been encouraged, if not actually developed, by Dr. McCann.

DR. McCANN: Dr. Morgan, there was one question which troubled the Board for years, about which I would like to comment, because I think the Regents should be aware of our difficulties. This is the matter connected with subspecialty certification. The creation of subspecialty certification has been the most troublesome single problem of the Board. We have certain organizations in tuberculosis, allergy, etc., that are not satisfied with our solution of the matter. Our Board has always held that subspecialty certification in cardiology, gastroenterology and chest diseases should be based on the general qualifications of an internist. In the case of allergy, I think we can see that the same thing is true, but an allergist might be an internist, he might be a pediatrician, he might be a dermatologist, and there is, perhaps, something to be said for the dissatisfaction among the allergy group, which is drawn from at least three sources instead of only one. I feel the weight of the College and the Regents should be thrown behind the Board in this matter, and that we should strive to prevent the independent formation of boards in subspecialties.

It is my guess that that movement comes from the fact that there are older men who have been long established in certain special fields of practice who feel that it would be impossible for them to take such examinations as the American Board gives, and yet they feel they want some special label attached to them. I believe it would be helpful if we could get some general statement which indicates that we do not feel that the important thing is to put a label on the older men. What we are trying to accomplish through this Board is to help mold the men who are coming up and who will occupy those positions in the future, and to see that they have a good, broad, firm and general foundation when they do that. They are the important ones, not the older men. I do not know how such a point of view could be presented to the profession as a whole, but it might allay some of this restlessness of which we see manifestations.

DR. MORGAN: The request is that the Committee on Educational Policy take under consideration this topic just discussed by Dr. McCann, relative to the establishment of subspecialty boards, to study the matter during the months ahead, and bring to the next meeting of the Regents in November a general statement of policy as an expression of the College relative to this problem. Unless there is some feeling to the contrary, the Chair will request that the matter be referred to the Committee on Educational Policy, Dr. William S. Middleton, Chairman, with the request that such a statement be formulated and presented to the Board of Regents at its November meeting for action.

We shall now have a report of the Committee on Educational Policy, Dr. William S. Middleton, Chairman.

Dr. Middleton reported that his Committee had received a panel relative to the succession of representatives of the American College of Physicians on the American Board of Internal Medicine, and the Committee had recommended the reappointment of Dr. Alex. M. Burgess and Dr. Truman G. Schnabel for terms of three years, to 1951, and the nomination of three individuals, one of whom shall be selected by the American Board of Internal Medicine to fill the unexpired term of Dr. William S. McCann, resigned, until 1950.

. . . The recommendations and nominations presented by Dr. Middleton's Committee were approved by resolution, and later Dr. Chester M. Jones was selected from the three nominees presented to succeed Dr. William S. McCann. . . .

DR. MORGAN: Next is the report from the Conference Committee on Graduate Training in Medicine, Dr. Reginald Fitz, Chairman.

DR. REGINALD FITZ: Dr. McCann has already said about everything the Committee has to say. Our Committee hopes to get the Council on Medical Education and Hospitals of the American Medical Association to hold a conference just before the annual meeting of the American Medical Association, and in that manner we hope that through the Council, the American Board and the College something more can be done than has been done heretofore.

DR. MORGAN: Next is the report from the Committee on the ANNALS OF INTERNAL MEDICINE, Dr. Francis G. Blake, Chairman.

DR. FRANCIS G. BLAKE: We have no report.

DR. MORGAN: May we have a report from the Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs?

DR. PINCOFFS: I received a communication from the Executive Secretary concerning the appointment of an Associate Editor in place of Dr. Gerald B. Webb, deceased, telling me that the Editor has the privilege of nominating a candidate to the Board of Regents. I should like to nominate Dr. James J. Waring to fill this vacancy.

. . . On motion by Dr. Walter L. Palmer, seconded by Dr. Alex. M. Burgess, and regularly carried, Dr. James J. Waring was appointed an Associate Editor. . . .

DR. PINCOFFS (continuing): I am glad to report that progress has been made in getting the ANNALS OF INTERNAL MEDICINE out on time, and that the circulation of the journal shows a most gratifying increase. At the present time we are printing 11,750 copies per month.

DR. MORGAN: That is an extraordinary figure for a journal in a special field.

May we now have the report of the Committee on Public Relations, Dr. James E. Paullin, Acting Chairman.

DR. PAULLIN: The Committee on Public Relations met at the Civic Auditorium, San Francisco, Calif., April 19, 1948, at 11:30 a.m.

#### I. Communications:

- (1) A communication from Dr. Edward M. Hayden, Tucson, Ariz., concerning the rebating from lay and professional laboratories to physicians in Tucson and Phoenix, Ariz., for services rendered by clinical laboratories and roentgenological and pathological laboratories.

The Committee wishes to advise Dr. Hayden that the problem which he presents should be handled at a local level by his county medical society.

The American College of Physicians is unalterably opposed to any practice of rebating fees or any other procedure which is contrary to the principles of medical ethics established by the American Medical Association, or any practice in conflict to the Hippocratic Oath.

It is advised that if Dr. Hayden finds that any member of the American College of Physicians participates in either the rebating or splitting of fees in his own community, if he will prefer charges against such member directly to the Board of Regents, that we will investigate such charges and either discipline or expel any member for conduct which in the opinion of the Board of Regents is derogatory to the dignity of the College or inconsistent with its purposes.

. . . On motion by Dr. James E. Paullin, seconded by Dr. LeRoy H. Sloan, and regularly carried, the above recommendation was adopted. . . .

DR. PAULLIN (continuing):

- (2) A communication from the American Association of Blood Banks requesting that the American College of Physicians approve their Constitution, a copy of which was enclosed, and that we endorse the purposes of their Association.

The Committee wishes to comment as follows: the consideration of such a request by the American Association of Blood Banks is beyond the scope and the purpose of the American College of Physicians. It is believed that the humanitarian program established by the American Red Cross fulfills all requirements of blood collection and distribution on a national level. This program has been endorsed by all national medical, dental, hospital and nursing organizations. It, to our mind, fulfills a national need. It does not in any way preclude the development of voluntary local programs.

- (3) A communication from the California Society of Internal Medicine re a resolution passed by the Council of the California Society of Internal Medicine, relating to the National Red Cross Blood Bank Program, in which the conduct of such a program is criticized as an infringement on free enterprise and that the Council disapproves such activity by the National Red Cross.

Your Committee believes that since the national blood donor program has received endorsement of the American Medical Association, the American Dental Association, the American Pharmaceutical Association, the American Hospital Association, the American Nurses Association, and all other humanitarian organizations, and since it does not in any manner preclude the development of local voluntary programs, we disagree with the sentiments expressed by the California Society of Internal Medicine.

... On motion by Dr. James E. Paullin, seconded by Dr. Francis G. Blake, and regularly carried, the above recommendation was adopted. . . .

DR. PAULLIN (continuing):

- (4) A communication from Dr. Edwin P. Jordan, of the Cleveland Clinic, to the Board of Regents, asking for information concerning the initiation fees and dues of members of that Clinic, in respect to their full-time participation in the Cleveland Clinic.

The Committee on Public Relations believes that the salary scale of the Cleveland Clinic is such that all members of the College connected with this and similar group organizations should be subject to the same initiation fee and dues as other members of the College in private practice. Since the Cleveland Clinic is operated on a non-profit basis and its surplus funds are devoted to postgraduate medical activities, it is suggested that in the event the initiation fee and dues should be a burden on any member of that Clinic, that the Foundation might give due consideration to defraying this expense, rather than the College giving a reduction of dues.

... On motion by Dr. James E. Paullin, seconded and regularly carried, the above recommendation was approved. . . .

DR. PAULLIN (continuing):

- (5) It is believed that since the compensation of members of the Armed Forces (Navy, Army, Public Health Service and Veterans Adminis-

tration) has been increased and since in many instances income from these positions is more than that of many members of the College engaged in private practice that an investigation should be made by a committee relative to a revision of the reduction in initiation fee and dues previously granted to members of these services.

. . . On motion by Dr. James E. Paullin, seconded by Dr. Maurice C. Pincoffs, and regularly carried, the above recommendation was approved, with the provision that the Committee on Public Relations, with the help of Mr. Pindar, make the survey. . . .

DR. PAULLIN (continuing) :

## II. Resignations:

- (1) *Dr. Reuben Hoffman (Associate), Henryton, Md.*

We recommend the acceptance of the above resignation.

- (2) *Dr. Arnold McNitt (Associate), Washington, D. C.*

We recommend the acceptance of the above resignation.

- (3) *Dr. J. Harold Root, F.A.C.P., Waterbury, Conn.*

We recommend the acceptance of the above resignation.

- (4) *Dr. H. Andrew Wallhauser, F.A.C.P., Wittman, Md.*

It is recommended that the resignation of Dr. Wallhauser be not accepted, but that his dues be remitted until he is able to resume the practice of medicine.

. . . On motion by Dr. James E. Paullin, seconded by Dr. Maurice C. Pincoffs, and regularly carried, the recommendations concerning resignations were approved.

DR. PAULLIN (continuing) :

## III. Fees and Dues Cases:

. . . Two cases were presented, one of a physician elected to Fellowship in the College in 1942, who six months thereafter entered military service but never completed taking up membership by the payment of the initiation fee of \$80.00. The Committee felt that consequently up to this time this man is not a member of the American College of Physicians, and suggested that the Executive Secretary inform him that because he has never paid his original initiation fee, he has never qualified for Fellowship in the College, and that should he desire to become a Fellow, he must pay the fee. Should he do this, the Committee would recommend that there be a waiver of dues extended to him for the years 1947 and 1948, because of ill health, and until he is able to resume the practice of medicine.

. . . The second case was of a Fellow for whom the Committee recommended the waiver of dues, beginning January 1, 1948, because of physical disability and retirement from practice.

. . . On motion by Dr. James E. Paullin, seconded and regularly carried, both recommendations were approved. . . .

. . . Continuing his report, Dr. Paullin presented the case of one Fellow who is more than two years delinquent in dues, and, therefore, subject to being dropped automatically from the Roster, in accordance with provisions of the By-Laws.

. . . On motion by Dr. James E. Paullin, seconded by Dr. David P. Barr, the report of the Committee on Public Relations was approved as a whole. . . .

DR. MORGAN: Next item on the agenda is the report of the Committee on Finance. Dr. Charles F. Tenney, Chairman.

DR. CHARLES F. TENNEY: The full Committee on Finance met on Monday, April 19, and reviewed all financial matters at this time before the College.

A. . . . Dr. Tenney proceeded to present a recommendation from the Committee that the retirement annuity of the Executive Secretary be increased, discussed the cost and stated that the Executive Secretary himself, under the College retirement plan, would have to contribute 20% of the cost. Numerous questions were asked by various members of the Board, including the amount of the present annuity, whether the Finance Committee had gone into all details, what happens if the annuitant's services terminate, by death or disability, etc. The Committee did not have immediately available all of the information suggested, and a resolution was adopted referring the matter back to the Finance Committee for further study and for a detailed report at the next meeting of the Board of Regents. . . .

DR. TENNEY (continuing):

B. Auditor's Report for 1947:

The Auditor's Report has been carefully examined, accepted and approved by the Finance Committee, and copies thereof have been prepared and are now being placed in your hands.

(1) Salient Data:

- (a) All accounts fully audited by Certified Public Accountant.
- (b) Increase in Funds:

	<i>Balance Jan 1, 1947</i>	<i>Increase (Net)</i>	<i>Balance Dec. 31, 1947</i>
General Fund . . . . .	\$234,159.26	\$36,411.56	\$270,570.82
Endowment Fund . . .	223,373.89	35,411.00	258,784.89
Bruce Fund . . . . .	10,000.00		10,000.00
Brower Fund . . . . .		2,500.00	2,500.00
	<u>\$467,533.15</u>	<u>\$74,322.56</u>	<u>\$541,855.71</u>

- (c) Gross Assets of the College—\$631,641.75.
- (d) On the Balance Sheet for 1947 operations, appears a balance of \$94.60, "Building Alterations Fund," which was established in 1946 for a certain third-floor improvement. That is a separate and distinct fund from the Building Fund, and since it has not been used to date, it may be applied in part against the deficit of \$153.88 of the Building Fund.
- (e) The Balance Sheet discloses two restricted current funds:

Chicago Postgraduate Fund . . . . .	\$ 443.30
Philadelphia Postgraduate Fund . . . . .	2,284.30

It was agreed by the Finance Committee that funds accumulated by the College from the Chicago Postgraduate Fund of \$443.30 and by the Philadelphia Postgraduate Fund of \$2,284.30, representing balances returned by directors of former courses, be closed out through the general accounts of the College and deposited in the current postgraduate account for use, inasmuch as they serve no practical purpose as restricted funds.

(f) Endowment Fund data:

Life Membership Fees, 1947, amounted to . . . . .	\$ 28,386.67
Profit on Investments . . . . .	16.00
Donation, Dr. A. Blaine Brower . . . . .	2,500.00

## (g) General Fund data:

Total Income .....	\$194,667.35
Total Expenses .....	151,139.01
Balance .....	<u>\$ 43,528.34</u>

In 1946 the balance was \$13,985.91. The net income for 1947 was nearly \$29,000.00 more than anticipated when budgets were prepared in the autumn of 1946, and the expenditures were \$15,000.00 less than budget provisions, exclusive entirely of the building program.

- (h) Detailed financial statements disclose all details and give a certified registry of all investments.

## C. Investment Counselor's Report and Recommendations:

- (1) Analysis, as of March 29, 1948 (excluding A. Blaine Brower Fund):

	<i>Endowment Fund</i>	<i>General Fund</i>	<i>Total</i>
Market Value .....	\$280,631.25	\$178,175.00	\$458,806.25
Book Value .....	266,788.11	156,076.42	422,864.53
Appreciation .....			<u>\$ 35,941.72</u>
Current average yield, 4.01%.			

- (2) Additional purchases of securities (Endowment Fund) since last meeting of the Board of Regents:

12-3-47 80 Shares, General Electric Co., common .....	\$2,846.49
3-29-48 2,500 U. S. of America Savings Bonds, Series "G", 2½s, 3-1-60 .....	2,500.00 *
	<u>\$5,346.49</u>

In accordance with regulations of the Board of Regents, the Committee requests approval of the above purchases, and I so move.

. . . The motion was seconded by William D. Stroud, and regularly carried. . . .

## DR. TENNEY (continuing):

As a matter of record, the Committee reports the purchase of the following securities for the General Fund:

12-3-47 20 Shares, E. I. du Pont, common .....	\$3,742.74
12-3-47 5,000 New York, New Haven & Hartford R.R. Co., Harlem River & Port Chester, First, 4s, due 1954 ...	4,912.50
12-3-47 20 Shares, Phillips Petroleum Co. ....	980.00
	<u>\$9,635.24</u>

- (3) The Finance Committee approves of the following recommendations of Drexel & Co. for sales and purchases of the following securities:

\* A. Blaine Brower Fund.



- (a) *Sell*—General Fund:
  - 30 Shares, American Telephone and Telegraph Co., Capital Stock
- Purchase*—General Fund:
  - 130 Shares, American Gas and Electric Co., common
- (b) Additional Investments:
  - Purchase*—Endowment Fund:
    - 5,000 Carolina, Clinchfield & Ohio Ry. Co., 1st “A”, 4s, 9-1-65
    - 4,000 Public Service Corp. of New Jersey, Perpetual, 6s
    - 5,000 Philadelphia Co., Coll. Tr., 4¼s, 7-1-61
    - 4,000 American Tobacco Co., Deb., 3s, 10-15-69 .
  - Purchase*—General Fund:
    - 60 Shares, Continental Insurance Co.
    - 100 Shares, Chrysler Corp.
    - 50 Shares, Timken Roller Bearing Co.
    - 25 Shares, Union Carbide & Carbon Corp.
    - 80 Shares, Phillips Petroleum Co.

The Committee asks specifically the approval of the above transactions which affect the Endowment Fund, and I so move.

. . . The motion was seconded by William D. Stroud, and regularly carried. . . .

DR. TENNEY (continuing) :

The Finance Committee has agreed to consult the Investment Counselor concerning the possibility of reducing from 31 to 25 per cent the present holdings of the College in Government Bonds. That is, at the present time 31 per cent of our investments are in Government Bonds, whereas the Committee desires further analysis by Drexel & Co. of the desirability of possibly reducing the proportion of Government Bonds in our portfolio from 31 to 25 per cent.

DR. MORGAN: It is the sense of this Board that it is the function of the Finance Committee, and we will entertain any recommendation relative to this problem, after you have made the study.

DR. TENNEY (continuing) :

D. General Comments :

The dues were increased (returned to the original rates) on January 1, 1947, and most of our members who served during the War returned to civilian status and, thus, resumed payment of dues during 1947. This, with some additions to membership, accounts for the following comparisons:

	1946	1947
Annual Dues .....	\$32,806.61	\$53,516.25
Initiation Fees .....	12,660.00	15,538.67
ANNALS, Subscriptions .....	50,625.30	62,435.59
Life Membership Fees are still keeping up, though not in excess of 1946:		
	1946	1947
Life Membership Fees received .....	\$28,495.15	28,386.67

## Annual Sessions, 1946 and 1947:

At the 1946 Annual Session there was a surplus of income over expenses of \$5,203.50.

At the 1947 Annual Session, there was a deficit of \$5,135.85, largely due to greatly increased expenses at Chicago over Philadelphia, partially arising from rental of exhibit space and increase of more than \$1,000.00 for the President's expenses and generally increased costs..

ANNALS OF INTERNAL MEDICINE comparison of the years 1946 and 1947 are as follows:

	1946	1947
Subscriptions .....	\$50,625.30	\$62,435.59
Advertising .....	23,661.69	26,246.07
	<hr/>	<hr/>
Expenses .....	\$74,286.99	\$88,681.66
	46,140.47	57,319.32
	<hr/>	<hr/>
Net Profit .....	\$28,146.52	\$31,362.34
	<hr/>	<hr/>

It is to be pointed out that the printing costs for the ANNALS is steadily and sharply rising, the comparison between 1946 and 1947 being \$31,179.00 for 1946; \$38,054.00 for 1947. Furthermore, there will be further increased basic printing costs in 1948 over 1947, because the last printer's increase became effective only on August 1, 1947. Additionally the Editor is now gradually increasing the size of the ANNALS, which will add materially to the cost.

. . . On motion by Dr. George F. Strong, seconded by Dr. Reginald Fitz, and regularly carried, the report of the Finance Committee was accepted as a whole. . . .

DR. MORGAN: Next is a communication from Dr. William S. Middleton.

DR. MIDDLETON: Mr. Chairman, the Committee on Educational Policy has under advisement a matter of serious importances to all of us, and I believe that the medical profession of the country looks to the American College of Physicians for guidance, for leadership in educational and research fields. With the present growth and knowledge of, and the prospect of an expansion in the application of, radioactive and stable isotopes, the Committee on Educational Policy feels there should be an active part played by this College. Therefore, it is recommended that research fellowships in the study of radioactive and stable isotopes in the field of biology and medicine be named and supported by the College in numbers not to exceed five. I move the acceptance of that recommendation.

DR. MORGAN: That would mean an expenditure of some ten or fifteen thousand dollars additional on research fellowships.

DR. TENNEY: I second the motion.

DR. PINCOFFS: I rise on a point of information. Has it been considered by the Committee how many opportunities with pay there already are for men who wish to go into this field? I am under the impression that there is a very generous allotment of Government funds covering many aspects in this field. Opportunities to go from paid positions in universities, or otherwise to carry on work for shorter or longer periods of time through fellowship or sundry other ways for which public funds are available, are far greater than the number of physicians who wish to enter this work. I may not be entirely accurate about this, however, and I should like to have information on it that would directly bear on whether we wish to expend College funds.

DR. MIDDLETON: There are two positions to be taken—first, opportunities do exist. These opportunities do not encompass the entire field, and there are vacancies currently that could be filled, were other funds available. That is the material aspect of it. The second aspect is from the standpoint of medical leadership; in these times with the incalculable range of application of these new skills, I believe the American College of Physicians would be remiss in not accepting this responsibility, and failing to enter this field specifically. That is to say, not in expansive terms, if there were not more than two places available, certainly we would not attempt to place five fellows. A maximum of five and certainly two or three such fellowships would be bread on the water.

DR. PAULLIN: I think all of us are in sympathy with Dr. Middleton's suggestion, but we have a Finance Committee that is requested to look after these expenditures, and when we recommend an appropriation of money, we are not quite certain our budget can withstand it. While I am quite sympathetic with this idea, at the same time I think it should be accepted in principle, subject to review by the Finance Committee, as to whether we can spend that much money. Our expenses in the College are getting terrible. This Annual Meeting here is going to be the most expensive we have ever had. We should look at our purse before we spend too much money.

DR. DAVID P. BARR: I was unable to take part in the discussions of this Committee on Educational Policy on this particular subject. I am sure that the importance of this method of study cannot be exaggerated, and I can see a certain advantage in the College taking the position of recognizing the need for such work. However, I have the feeling that almost every field of investigation is going to be permeated with the use of isotopes, including most of our regular research fellows. There is a question as to whether it is appropriate to separate those fellowships which have to do with the use of isotopes and those that have to do with medical research in general.

I happen to know something about the provisions which are being made for study by the Atomic Energy Commission—and other agencies—for this type of work. I have the feeling, as to our own institution, that just as fast as the young men are ready to engage in this field, they will find unusual and ample opportunities for support from the Atomic Energy Commission. That, as Dr. Pincoffs pointed out, would be not only for the use of the Governmental laboratories in different parts of the country, but also for fellowship salaries. I do not believe I would be in a position to concur in this recommendation.

DR. FITZ: My mind reacts as did Dr. Barr's. I think it is a great mistake, from the point of view of fellowship policy, to separate the funds. I would much rather have the fellowships set up as they are now, and if a man came along who was properly qualified and wished to work in this field, grant him one of our ordinary fellowships. I think it would prove narrow-minded, in the long run, to specify exactly what kind of work one of our fellows should enter.

. . . The Chair at this point, forgetting that the motion had already been seconded, inquired if any one would second the original motion. There was no such second, and the Chair declared the motion failed for lack thereof. . . .

DR. MORGAN: I think, Dr. Middleton, certainly our experience during this next year, the experience of the Committee on Fellowships and Awards, will be useful, and I think we might well reintroduce such a motion at our next meeting, if applications this year indicate the demand over and above that which we can meet with our regular appropriated funds for fellowships.

We must now consider the recommendation made by the Committee on Credentials at the November, 1947, meeting, embodying two recommendations. The first was the Committee realizes that the number of applicants for admission is growing steadily. The question comes up from time to time about a candidate who is not an internist, but is a neuropsychiatrist, a dermatologist, or some other affiliated specialist. The informative booklet of the College says that membership need not be made up only of internists, but may include those properly qualified in pediatrics, neurology,

psychiatry, public health, radiology, and so forth. The Committee believes it would be well seriously to consider changing our regulations and limiting membership to those who are internists, and to discontinue, after a certain time, to take in men who are not internists, even though they be engaged in affiliated specialties.

This would exclude dermatologists, pediatricians, and a few others.

The second has to do with requiring certification by the American Board of Internal Medicine, or an allied Board, such as the American Board of Pathology, before a candidate is eligible for Associateship.

I suggest that the Board of Regents take action on these two matters at this meeting, because of the increasing size of the College and the inevitable limit in the size of the College, membership shall be limited to those who are internists and we shall not accept men, even though they are qualified by their respective boards, in dermatology, neuropsychiatry or radiology. Do I hear a discussion relative to this proposal from the Committee on Credentials?

DR. ALEX. M. BURGESS: Will you further elaborate on the affiliated specialties that would be excluded? You mention dermatology, pediatrics, neuropsychiatry, and, I recall in some previous discussion, something was said about not excluding pathologists and clinical pathologists.

DR. PINCOFFS: I make a motion that the American College of Physicians shall not accept as qualifications for membership certification by the American Boards of Dermatology, of Pediatrics, of Neurology and Psychiatry, and of Radiology.

DR. A. B. BROWER: I second the motion.

DR. WALTER L. PALMER: I rise to question what is the proper procedure in the College. On Sunday afternoon this was discussed with the Regents and the Governors. Last year a similar question was discussed with the Governors. Where do the Governors come in, or where should we come in on these questions?

Now it seems to me if the Regents want to act on these questions without consulting the Governors, if that is the policy of the College, it is all right, but on the other hand, if they do wish to consult the Governors on these two questions, then I think they should give the Governors an opportunity to discuss those two questions and make a recommendation to the Regents. Of course, if you did that, the Regents might be confronted with the situation of wanting to overrule the Governors. I think procedure-wise it would be better to let the Governors discuss this first.

DR. MORGAN: Your point is well taken.

DR. GEORGE MORRIS PIERSOL: It is on their agenda. They have the question of whether these matters will involve a revision of the Constitution and By-Laws. The proper way might be to have it handed over to the Committee on Constitution and By-Laws and invent the machinery for it. All we can do today would be to pass a motion in which we recommend the modification of the By-Laws, which will require another year at least to put into effect. In the meantime, the Governors have the same problem. The Committee on Constitution and By-Laws would have to be governed by the joint action of these two bodies.

DR. BROWER: I would like to move that you lay this motion on the table, until after the meeting of the Board of Governors tomorrow.

DR. PAULLIN: I second the motion.

. . . The previous motion was withdrawn, the new motion put to vote and carried. . . .

DR. MORGAN: I think the Chair will rule that the second point belongs in the same category and will not be acted upon until the Governors have had a chance to discuss it further.

DR. PIERSOL: I feel strongly that the ideas of the Governors should be solicited on these points. I might say, in connection with the second one, since that recommendation was made, members of our own Committee have been very definite in their suggestions that perhaps another way out of the difficulty would be to increase the age limit for admission to Associateship; another suggestion was that it might

be well to increase the period of Associateship during which a man may qualify for Fellowship. Both of these would to some extent solve the difficulty. Then a final suggestion was made to me by some distinguished members of this Board—it is shocking, but in the end it is what will have to happen and will happen—and that is that we cut the Gordian knot and abolish Associateship, and merely have requirements for admission to Fellowship, based on whatever requirements or qualifications, which obviously will include certification, the Board of Regents may specify.

Several distinguished bodies have had groups of Associates and within the last few years have come to the conclusion that it is unsatisfactory and cumbersome, and that the best plan is to wait until a man is qualified for admission wholly into the organization as a Fellow. This idea has merit, and, in the long run, I personally believe it will add to the dignity of this group. I am firmly convinced that the day is not too far off when that will be the solution of our problem.

DR. MORGAN: With your permission, Dr. Piersol, we shall then defer action at this meeting on the second item. This certainly has to do with the most important functions of the administration of this College, and I know that your insistence upon action stems from difficulties you have had.

I wonder what you think of this suggestion—that after the Board of Governors consider these two matters tomorrow, that you convene your Committee on Credentials together with the Executive Committee of the Regents a day early in the autumn and spend the entire day going over this matter, with the hope that out of such a meeting would come solid recommendations which the Board of Regents could act upon? I offer it as a suggestion for the incoming administration.

DR. PIERSOL: That is a good suggestion.

DR. GEORGE F. STRONG: I would like to elaborate further on what Dr. Palmer said. I served on the Board of Governors, and I know the feeling of inadequacy or ineffectiveness of that group is very real. It seems to me that as a matter of policy, and in the best interests of the College, it would be wise if there was a division of responsibility in this matter. It is the Governors essentially who pass on the names that are proposed for Associateship and Fellowship. It is the function of the Governors to consider what the requirement for those Associates and Fellows should be. We should delegate matters having to do with requirements and qualifications to the Governors, and give them a sense of responsibility.

. . . Dr. James E. Paullin arose to speak personally to the Regents at this time, marking his last day's membership on the Board of Regents, after many years of service, but at his own request his comments were not recorded. . . .

DR. MORGAN: Dr. Paullin, I join the group in a rising vote of abiding affection. (Applause.) The meeting is adjourned.

. . . Adjournment, 3:15 p.m. . . .

Attest: E. R. LOVELAND,  
*Executive Secretary*

## ANNUAL BUSINESS MEETING

SAN FRANCISCO, CALIF.

APRIL 22, 1948

The Annual Business Meeting of the American College of Physicians was called to order at the Civic Auditorium, San Francisco, Calif., April 22, 1948, at 2:00 p.m., with President Hugh J. Morgan presiding, and with Mr. E. R. Loveland acting as Secretary.

PRESIDENT HUGH J. MORGAN: I declare that there is a quorum present and that the Annual Business Meeting is in order. The Secretary, Mr. E. R. Loveland, will read the abstract of the Minutes of the preceding Annual Business Meeting.

... Mr. E. R. Loveland read the abstract of the Minutes, which by resolution was approved as read. ...

PRESIDENT MORGAN: We shall have the annual report of the Treasurer, Dr. William D. Stroud.

DR. WILLIAM D. STROUD: Mr. President, Fellows and Masters of the College—The details of all operations of the College for 1947, along with the certified public accountant's audit, will be published to the members through the *ANNALS OF INTERNAL MEDICINE*. During the year 1947 the College added to its General Fund \$36,411.56, to its Endowment Fund \$35,411.00, and received a gift in trust of \$2,500.00, an initial deposit on an educational trust fund of \$10,000.00 subscribed by one of our Fellows, Dr. A. B. Brower. The gross assets of the College, as of December 31, 1947, amounted to \$631,641.75—\$270,570.00 is in the General Fund and \$271,284.00 is in the Endowment Fund, and the balance represents real estate, furniture and equipment.

The College operated entirely within its budget for the year. Its investments are carefully watched by our Investment Counselor and the Committee on Finance, and our investment accounts are in a favorable condition. As of December 31, 1947, the College held investments at book value totalling:

Endowment Fund .....	\$266,788.11
General Fund .....	156,076.42
	<hr/>
	\$422,864.53
	<hr/>

The current market value of these securities is \$458,806.25, showing an appreciation of \$35,941.72. The current average yield on our securities is 4 per cent.

The Board of Regents has approved a budget for 1948 calling for an estimated income of approximately \$194,000.00, and an estimated expenditure of approximately \$153,000.00, leaving an anticipated balance of \$41,000.00. The financial policies of the College are directed along conservative lines.

... On motion made, duly seconded and carried, the report of the Treasurer was accepted. ...

PRESIDENT MORGAN: Next is the report of the Executive Secretary, Mr. E. R. Loveland.

MR. E. R. LOVELAND: Mr. President, Fellows and Masters: My report is supplementary to those of the Treasurer, the Secretary-General and the President. During the recent war 35 per cent of our members were in the Armed Forces; they have practically all returned to civilian activities and their resumption of active membership.

There has been a marked increase in the interest of younger physicians who are aspiring to membership in the College, and this will be reflected in a materially growing number of candidates for Associateship.

During 1947 there was a continued increase in the volume of College activities. The circulation of the *ANNALS OF INTERNAL MEDICINE* grew 15 per cent, this increase coming not only from physicians in the United States but from other countries throughout the world. The circulation is now over 11,600 copies per month.

Since the last Annual Session of the College, we have conducted twenty-one formal Regional Meetings, largely of the single State character, but in some instances of the multi-State character. These meetings are of a more intimate type than the Annual Session; they give an opportunity for closer acquaintanceship in each Governor's territory, present an opportunity for younger members to present papers and, in many instances, for the local members to meet and observe younger physicians who are being proposed for Associateship.

Due to labor conditions and a continued shortage of paper, we have not been able to republish the complete Directory of the College, but have, by direction of the Board of Regents, substituted Membership Rosters. A new Membership Roster for 1948

is in process of publication, and will be ready for distribution in the late summer. Those who have not returned the data forms for the new Roster are requested to do so without further delay.

For the last few years the College Building in Philadelphia has been inadequate in size for the growing activities and increased staff. One year ago your Board of Regents, through the House Committee, authorized an addition to the building, which was begun during September and is now completed, which provides us with superb working facilities and is an addition of which the College is justly proud. Our members again are cordially invited to visit the College offices whenever they are in Philadelphia. Your Executive Secretary and his staff are deeply gratified with the cordial relations and the oft expressed appreciation of its work by the members at large, which is a constant stimulation to greater effort and an increased desire to serve them more efficiently in all ways possible.

I have just received from the Registration Desk a report that the total registration at this moment is 3,083, of which 487 are ladies.

PRESIDENT MORGAN: May I suggest a rising vote of appreciation and thanks to Mr. Loveland?

. . . Rising vote of approval and thanks to Mr. Loveland. . . .

PRESIDENT MORGAN: And may I add that Mr. Loveland is an educational and business administrator extraordinary.

The next item on the agenda is the annual report of the Secretary-General, Dr. George Morris Piersol.

DR. GEORGE MORRIS PIERSOL: Mr. President, Officers, Regents, Governors, Masters and Fellows of the College:

*Membership:* Since the last Annual Session of the College, there have been elected 5 Masters, 211 Fellows, and 388 Associates, which brings the total membership to 6,250, divided as follows:

11 Masters
4,567 Fellows
1,672 Associates
<hr/>
6,250 TOTAL
<hr/>

*Life Members:* During the past year 96 Fellows have become Life Members of the College, bringing the total to 708, of whom 51 are deceased, leaving a balance of 657.

*Deaths:* It is with regret that we report the deaths of 2 Masters, 80 Fellows and 5 Associates during this period. Their names and records have been recorded in the archives of the College.

*Postgraduate Courses:* The Advisory Committee on Postgraduate Courses has continued its activities, in many cases expanding our courses to new fields. Through their efforts there were organized 21 separate and distinct courses during 1947, and there are 9 courses on the spring program of 1948. There is a very satisfactory registration for all of the current courses. Approximately one thousand doctors attend the College courses each year, evidencing the popularity and value of this feature of the College activities.

*Fellowships:* A further important educational activity of the College has been the creation and extension of Research Fellowships. Approximately \$20,000.00 per annum is allocated to these fellowships. Seven new fellowships have been awarded to begin on July 1, 1948.

As gratifying as are the above mentioned educational activities of the College, it should not be overlooked that the most significant and far-reaching contribution of the College is its Annual Session. These have been marked by progressively improved

programs and ever widening scope. The current session is a further outstanding example of what may be accomplished by a year's well coördinated effort. The College is mindful of its great debt to those who have made this San Francisco Session possible.

. . . . .

Now, Mr. President, throughout this past year, as President of the American College of Physicians, you have guided the destiny of this organization and you have carried out its purposes with good judgment and exceptional ability. Those of us whose privilege it has been to be closely associated with you in the conduct of the College are keenly aware of the never failing courtesy, forbearance and coöperation that have marked your every act. Therefore, it is our desire to express to you in some enduring way our appreciation and affection, and so, on behalf of your fellow Officers, the Regents and Governors of the American College of Physicians, it is our pleasure to present to you this gavel. (Applause.)

PRESIDENT MORGAN: Dr. Piersol, thank you and through you the Officers, Regents and Governors and Fellows of this College. This gavel constitutes a souvenir of the most important and I hope most useful year of my life.

It is now my great pleasure to present to you our new President. I first knew him when he came to Baltimore from active duty with the Medical Department of the Army after World War I to help Dr. Sydney Thayer, Professor of Medicine, organize the Department of Medicine. He not only taught Clinical Medicine at Johns Hopkins with Dr. Thayer, but he also developed there an extraordinary laboratory for clinical investigation in the biochemistry of metabolic diseases.

He has degrees from Amherst, Harvard and Columbia, and at one time or another has worked at the Massachusetts General Hospital, the Hospital of the Rockefeller Institute, the Johns Hopkins Hospital of Baltimore and the Presbyterian Hospital in New York. He was the Bard Professor of Medicine at Columbia until he retired to assume his present position as Director of the Public Health Research Institute of the City of New York.

It is an honor to present to you the President of the College, Dr. Walter W. Palmer. (Applause.)

. . . Dr. Walter W. Palmer assumed the Chair. . . .

PRESIDENT WALTER W. PALMER: Members of the College, I wish to express my keen and sincere appreciation of the honor which you have conferred. I assume the duty as President of this distinguished College with a great deal of trepidation. I am following a man who has set a precedent that is going to be impossible to excel and most difficult to equal.

We have had here in San Francisco an unusual and an extremely gratifying experience. It is, I think, the best meeting I have ever attended. That is a great inspiration for us who will try to put on an Annual Session next year in New York.

I shall attempt to outline the future policies. We are living in a time when future policies and plans are likely to be interrupted. It is not easy to make long term plans with the world and this country in the present situation. One has only to glance at our newspapers, or listen to the radio; on the whole, it is most depressing. However, as physicians, we should not be depressed, but should do our duty. Mainly, we shall have to change this year, or the next, or some time in the future, from the business that we love to more urgent and pressing duties.

Certainly with the extraordinarily well organized committees, headed by our remarkable Executive Secretary, the American College can go on without any interruption. The wonderful educational program which has been developed over the past—the Regional Meetings, the Postgraduate Courses—should be as good or better than in the past. The first activities have not been extensive, but they have been valuable and important. All of you have attended these Regional Meetings, programs



and dinners, and you will realize, I am sure, how important the progress of medicine is and how dependent on research in the basic sciences.

We are all aware of the fact that there are now enormous sums devoted to the study of cancer—millions for cancer, millions for poliomyelitis, and large sums for the study of the diseases of old age. These sums are drawing into the field large numbers of investigators, and they are going to announce the results of their investigations, and the duty falls upon this College to try to get these results before its members as rapidly and in as good form as possible. This will be one of our duties next year, and a more important duty, perhaps, than before, because the numbers are greater, they are working longer and we may expect more results than in the past.

There is a feature of this development in this country that has a sobering effect upon men who are interested in investigation. Of the money given for specific purposes, as indicated by what I have said, there is a very important division in the field of the sciences which is having a harder time in spite of all the money now available. This is the man who is finding his haven in the university engaged in the basic materials, not on any project that is handed to him, but he is following his own fancy, the dictates of his own interest. Such a man has to depend upon university funds to a large extent—the small budget developed by the university for teaching. Universities are having a hard time, despite the money available for these things, and something is necessary, in order to relieve their anxiety. The money that used to go to the universities now goes into the tax pots. We must, I feel, look to tax money to help us out in research in the basic fields.

It was my privilege to serve on the medical committee with Dr. Vannevar Bush, who, at the request of President Roosevelt, made that very interesting and valuable report to President Truman on the need for a National Research Foundation to supply the need, the support for basic science work. This report, after battling about in Congress for a couple of years, finally was passed last year but vetoed by President Truman, because it didn't conform to certain Government precedents in the matter of organization.

I believe that this matter is so important that the obstacles presented in it—and I may say, based upon Dr. Vannevar Bush's report—will be removed, and we shall have a National Science Foundation which will support the men whom I consider so very important. I think they are the most important in our progress, not only in medicine, but in science in general. Thank you! (Applause.)

\* \* \*

We shall proceed with our agenda and ask the Secretary to present an amendment to the Constitution, this amendment having already been approved by the Board of Regents, and is now subject to approval of the Fellows and Masters of the College.

MR. LOVELAND: The By-Laws of the College were amended last year at the annual session, and, among other things, there was provided a new Article VI for the election of Masters, in which it is specified "A special Committee on Masterships will be named by the President. . . ." It was overlooked at that time that in the Constitution, Article IV (b), a minor amendment should be made changing the wording from "Committee on Credentials" to "Committee on Masterships," which makes the revised paragraph read as follows:

"(b) Masters. Masters of the American College of Physicians shall be those who have attained the rank of Fellows, and who on account of personal character, positions of influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships to the Board of Regents for special and well-earned distinction. Such Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M.A.C.P. in connection with scientific publica-

tions, at professional and academic functions and in connection with their professional activities.

Masters shall have the right to vote and to hold office."

PRESIDENT PALMER: You have heard the recommendation for the amendment to the Constitution. What is your pleasure?

. . . A motion was made to approve the amendment. It was duly seconded, voted upon and carried. . . .

PRESIDENT PALMER: Next on the agenda is the report of the Committee on Nominations by its Chairman, Dr. William D. Stroud.

DR. WILLIAM D. STROUD: Mr. President, Officers, Fellows and Masters of the College: In accordance with the provisions of the Constitution and By-Laws, the Nominating Committee has placed in nomination and has published in the ANNALS OF INTERNAL MEDICINE the names of the nominees to the elective offices, and at this time will place in nomination the following names for the Board of Regents and Board of Governors. These nominations do not preclude nominations that may be made from the floor:

*Elective Offices:*

President-Elect . . . . . Dr. Reginald Fitz, Boston, Mass.  
 First Vice President . . . . . Dr. William S. Middleton, Madison, Wis.  
 Second Vice President . . . . . Dr. Maurice C. Pincoffs, Baltimore, Md.  
 Third Vice President . . . . . Dr. Charles E. Watts, Seattle, Wash.

PRESIDENT PALMER: You have heard the nominations for the elective offices of the College. Are there any nominations from the floor, and what is your pleasure?

. . . It was moved and seconded that the nominations for the Elective Offices be closed, and that the Secretary be instructed to cast the ballot for the election of the above nominees. . . .

DR. STROUD (continuing): The Nominating Committee places in nomination the following names as members of the Board of Regents, for term expiring 1951:

Dr. Hugh J. Morgan . . . . . Nashville, Tenn.  
 Dr. Walter B. Martin . . . . . Norfolk, Va.  
 Dr. LeRoy H. Sloan . . . . . Chicago, Ill.  
 Dr. George F. Strong . . . . . Vancouver, B. C., Canada  
 Dr. Marion A. Blankenhorn . . . . . Cincinnati, Ohio

PRESIDENT PALMER: You have heard the nominations for the Board of Regents. Are there any nominations from the floor, and what is your pleasure?

. . . It was moved and seconded that nominations for the Board of Regents be closed, and that the Secretary cast the ballot for the election of the nominees above named. The motion was voted and carried. . . .

DR. STROUD (continuing): The Nominating Committee places in nomination the following names for the Board of Governors, for term expiring 1951:

Dr. E. Dice Lineberry, Birmingham . . . . . ALABAMA  
 Dr. Leslie R. Kober, Phoenix . . . . . ARIZONA  
 Dr. Lemuel C. McGee, Wilmington . . . . . DELAWARE  
 Dr. William C. Blake, Tampa . . . . . FLORIDA  
 Dr. Carter Smith, Atlanta . . . . . GEORGIA  
 Dr. Samuel M. Poindexter, Boise . . . . . IDAHO  
 Dr. Walter L. Palmer, Chicago . . . . . ILLINOIS (Northern)  
 Dr. J. Murray Kinsman, Louisville . . . . . KENTUCKY  
 Dr. Richard S. Hawkes, Portland . . . . . MAINE  
 Dr. Wetherbee Fort, Baltimore . . . . . MARYLAND  
 Dr. John G. Archer, Greenville . . . . . MISSISSIPPI

Dr. Harold W. Gregg, Butte .....	MONTANA and WYOMING
Dr. Robert O. Brown, Sante Fe .....	NEW MEXICO
Dr. Asa L. Lincoln, New York .....	NEW YORK (Eastern)
Dr. Charles A. Doan, Columbus .....	OHIO
Dr. Howard P. Lewis, Portland .....	OREGON
Dr. David W. Carter, Jr., Dallas .....	TEXAS
Dr. Karver L. Puestow, Madison .....	WISCONSIN
Dr. Rafael Rodriguez-Molina, San Juan ...	PUERTO RICO
Dr. Charles H. A. Walton, Winnipeg .....	MANITOBA and SASKATCHEWAN
Dr. John W. Scott, Edmonton .....	ALBERTA and BRITISH COLUMBIA

PRESIDENT PALMER: You have heard the nominations for the Board of Governors. Are there any nominations from the floor, and what is your pleasure?

... It was moved and seconded that nominations for the Board of Governors be closed, and that the Secretary cast the ballot. The motion was voted and carried. ...

PRESIDENT PALMER: It is now my pleasure to ask Dr. F. Gorham Brigham and Dr. Alex. M. Burgess to escort Dr. Reginald Fitz, the new President-Elect, to the platform.

It is a great pleasure to introduce Dr. Fitz, of Boston, as your President-Elect.

DR. REGINALD FITZ: Mr. President, Fellows and Masters of this College, I am sure I feel just exactly as you all must feel who have been elected to office in this College. In electing me as your President-Elect, you have paid me one of the highest compliments that could possibly come to any doctor in this country in this day and age. All I can do in accepting this office is to pledge myself to carry forward the ideals and the work of the College during the next succeeding year. I thank you all for the honor you have given me. (Applause.)

PRESIDENT PALMER: I should like to announce that the 1949 Annual Session will be held in New York City, March 28-April 1.

Are there any resolutions to be presented?

DR. T. GRIER MILLER: Mr. President, Masters and Fellows of the College, I wish to present the following resolution of thanks, and to move that it be spread on the Minutes of this meeting:

"RESOLUTION OF THANKS to our distinguished leader and President, Dr. Hugh J. Morgan, for the inspiration of his guidance during the past year, as well as during this Annual Session; to his Chiefs of Staff, General Chairmen William J. Kerr and Ernest H. Falconer, for a magnificent program; to the Chairmen of their local Committees, Dr. Sidney J. Shipman, Chairman of the Committee on Entertainment; to Dr. Dwight L. Wilbur, Chairman of the Committee on Clinics; to Dr. George S. Johnson, Chairman of the Committee on Hotels and Transportation; to Dr. Roberto F. Escamilla, Chairman of the Committee on Panel Discussions; to Dr. William C. Voorsanger, Chairman of the Committee on Publicity, and to the individual members of each of those Committees;

To Mrs. Stacy R. Mettier, Chairman of the Ladies' Entertainment Committee, and to all of her worthy and capable colleagues, Mrs. Sidney J. Shipman, Mrs. Roberto F. Escamilla, Mrs. William J. Kerr, Mrs. Ernest H. Falconer, Mrs. J. C. Geiger, Mrs. Edward Matzger, Mrs. William C. Voorsanger, Mrs. Dwight L. Wilbur, and all the others who have so ably and graciously taken care of the visiting ladies;

To Mr. Daniel Wilkes of our Press Office and to the public press; to Mr. Walter G. Swanson, Vice President and General Manager of the San Francisco Convention and Tourist Bureau, and Dr. Harold G. Trimble of the Entertainment Committee who so kindly handled the distribution of the tickets for the Concert on Monday evening; to all of these and many others, individually and

collectively, our heartfelt thanks again for their generous hospitality in full measure—pressed down and running over.”

PRESIDENT PALMER: I would like to see a rising expression of enthusiasm for this resolution, a standing vote.

. . . A rising vote of applause was given in favor of this resolution. . . .

PRESIDENT PALMER: If there is no other business to come before this meeting, I declare it adjourned.

Adjournment—2:45 p.m.

Attest: E. R. LOVELAND,  
*Executive Secretary*

## ABRIDGED MINUTES OF THE BOARD OF REGENTS

SAN FRANCISCO, CALIF.

APRIL 23, 1948

The concluding meeting of the Board of Regents, held during the 29th Annual Session at San Francisco, Calif., was called to order at 1:00 p.m. in Room 203 of the Civic Auditorium on April 23, 1948, with President Walter W. Palmer presiding, and Mr. E. R. Loveland acting as Secretary. Roll call revealed the following in attendance:

Walter W. Palmer, *President*; Reginald Fitz, *President-Elect*; Maurice C. Pincoffs, *Second Vice President*; T. Grier Miller, Charles F. Moffatt, Charles F. Tenney, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, George F. Strong, Walter L. Palmer, *Chairman, Board of Governors*.

. . . Reading of the Minutes of the preceding meeting of the Board of Regents was dispensed with. . . .

PRESIDENT WALTER W. PALMER: We shall have the report of the Committee on Nursing, Dr. Francis G. Blake, Chairman.

Dr. Blake is unable to be here, and since I was present at the meeting, I shall read Dr. Blake's report:

“The Committee on Nursing Service held a meeting at New Haven, Conn., on Tuesday, March 30, 1948. Dr. Walter W. Palmer, Dr. Thomas P. Murdock and Dr. Francis G. Blake, Chairman, were present. An invitation had previously been extended individually to Dr. Howard C. Naffziger, Chairman, and to Dr. Harold L. Foss and Dr. Leland S. McKittrick, members of the corresponding Committee of the American College of Surgeons, to attend the meeting, but they were unable to be present.

“For the information of the Committee, Dr. Murdock, Chairman of the Committee on Nursing Problems of the American Medical Association, reviewed in detail the extensive studies of nursing which have been conducted by the A.M.A. Committee, and the facts, opinions and proposals derived from joint meetings and conferences of this Committee with leaders in the educational, administrative and public health fields of the nursing profession, representatives of the American Hospital Association, the American College of Surgeons, the American Nurses Association, and other interested and informed persons.

“As a result of these studies, the Committee of the American Medical Association has arrived at tentative conclusions concerning the requirements for nurses during the coming decade and is preparing a series of recommendations devised to solve current problems. It is expected that the report of this Committee will be completed and ready for presentation in June.

"The Committee of the College finds itself in general agreement with the tentative conclusions and proposed recommendations of the A.M.A. Committee, but feels that it would be inappropriate to report further on them at this time, prior to their publication. It also is of the opinion that the studies, conferences and recommendations reported to us by Dr. Murdock have been so comprehensive and valuable that little of significance could be added by the Committee of the College. It is, therefore, recommended that the Committee be discharged.

"Respectfully submitted,

Thomas P. Murdock

Walter W. Palmer

Francis G. Blake, Chairman"

What is your pleasure regarding this report?

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. Ernest H. Falconer, and regularly carried, the above report was adopted. . . .

. . . In accordance with regulations of the Constitution and By-Laws, and additional previous resolutions of the Board of Regents, Dr. George Morris Piersol was reelected Secretary-General, Dr. William D. Stroud was reelected Treasurer, and the various standing Committees were appointed. (The lists and personnel of these Committees have been published elsewhere and are not herein repeated.) . . .

. . . Dr. Franklin M. Hanger, Jr., of New York City, was appointed by the Board of Regents as the General Chairman for the 1949 Annual Session. . . .

. . . Inasmuch as there appeared no real occasion for the continuance of the Council for Study, Prevention and Treatment of Rheumatic Fever, that Council was discontinued. . . .

PRESIDENT PALMER: We shall proceed with the agenda. The next is the report from the Board of Governors, Dr. Walter L. Palmer, Chairman.

DR. WALTER L. PALMER: There are two items that came before the Board on Wednesday which may be of some interest to the Board of Regents. The first was the discussion and action on the motion that Dr. Edgar V. Allen introduced last year, as a result of which a Committee of Five was appointed to discuss the procedure governing the election of Governors, getting the sentiment of members in each district, and so forth. The net results of the discussion of some forty minutes by the Governors was that the Board voted about three to one to allow things to stand as they are.

The other item which received a great deal of discussion was the report of the Committee on Credentials, with regard to two special recommendations—one regarding the discontinuance of taking members outside of internal medicine. Dr. Alex. M. Burgess kindly consented to be present at the meeting of the Board of Governors as an Alternate for Rhode Island, and Dr. Wallace M. Yater, a member of our Credentials Committee, was there as the Governor for the District of Columbia. The Board finally voted, at least three to one, against the restriction of pediatricians, neuropsychiatrists, etc. In other words, the Board does not approve of the limiting of the College to those interested only in internal medicine.

Then with regard to the other recommendation of the Committee on Credentials, namely, that certification be a prerequisite for Associateship, there was a great deal of discussion, and again the Board voted against that recommendation. There was still another item of interest growing out of Dr. Chester S. Keefer making the suggestion that Associateship be eliminated altogether. Dr. Alex. M. Burgess supported that position, and finally, for the sake of getting some indication of sentiment among the Governors, a resolution was adopted that the present feeling of that Board was that Associateship should eventually be discontinued, and that resolution was supported almost three to one, although there were several members who did not vote. It was purely an expression of opinion.

Then it was moved by Dr. Turner Z. Cason, of Florida, and discussed that the

Board of Governors recommend to the Board of Regents that a Committee be appointed to study this whole problem thoroughly again, and bring in a subsequent report. Someone pointed out that that had been going on since 1944, and I remarked that I thought that some day the Board of Regents would want the Board of Governors to make up their minds as to what it wants. The reply was "we want another year, and we would like to have this Committee study it thoroughly, and we, the Governors, would like to have another opportunity to express our opinions on it." I pointed out that the Regents had at the last meeting decided to appoint a Committee who would report at a meeting this coming autumn. The Governors however felt, Mr. President, that they would like to have another "go" at it before the Regents finally take action.

Was there anything else, Mr. Loveland?

MR. LOVELAND: There was another item that might be expanded upon, namely, the proposal by Dr. Edgar V. Allen's Committee of a year ago. You will recall that Dr. Allen's motion before the Board of Governors was to democratize the College and its methods of selecting Governors, Regents and Officers. He hoped to present a method of having the members elect their own Governors from their particular territories, the Governors possibly electing the Regents and the Officers. The Committee appointed by the Chairman of the Board of Governors reported to the Board, through its Acting Chairman, Dr. Benjamin F. Wolverton, of Iowa, and presented a very mild and perfectly harmless suggestion, by which the present system, as prescribed by the By-Laws, might be augmented through consulting the Fellows to a greater degree concerning the selection of the Governors, but in no way restricting the action of the Nominating Committee. The Board of Governors, however, as a whole, appeared suspicious of any proposal, and it voted down even this mild suggestion. They would have no part in changing the present system.

DR. WALTER L. PALMER: That is very properly stated, and the vote was at least three to one against the proposal. The Governors indicated very great fear of politics appearing if anything of that sort were adopted.

PRESIDENT PALMER: It has been suggested, and very properly so, that the Minutes of the Board of Governors' meeting shall be abstracted carefully and a copy sent to each member of the Board before we take up the several points which Dr. Palmer has brought up.

According to the Board of Governors, it would be proper that we appoint a Committee which would have on it representation from the Board of Governors to continue the study of the proposals of the Committee on Credentials.

DR. MAURICE C. PINCOFFS: Will this Committee deal exclusively with the proposal that Associateship be dropped, or with all aspects?

PRESIDENT PALMER: With all aspects, I think.

The next item is the selection of the 1950 meeting place. As you know, New York has already been selected for 1949. Will the Secretary report on some of the information we have gathered during a recent canvass of the Board of Regents?

MR. LOVELAND: Those who have been on the Board of Regents previously know that when the matter of selecting a city for 1949 came up, the schedule in various cities was very nearly filled, and they refused to hold open dates until the San Francisco Meeting; thus, the Regents had to be canvassed by mail, and after two or more such efforts, New York was selected for 1949. We are now requested to select our meeting place for 1950. It is quite apparent, under present conditions, that we must work two years ahead on the Annual Session.

The principle involved in the mail vote, which, perhaps, was not wholly understood, was whether the College should not alternate its Annual Meetings between the east and midwest, and occasionally the far west, or in Canada. It was thought that if New York were selected for 1949, the 1950 meeting might be held in the midwest; if the 1949 meeting went to the midwest, the 1950 meeting would be in the east.

Two of the chief contenders for the 1949 and 1950 meetings were New York and Boston. Boston wanted the meeting in 1950 and New York in 1949. In our final survey of the Regents, there were six who thought we should meet in New York in 1949 and in the midwest in 1950, adhering to our former plan of alternating the territory. There were only five who voted for St. Louis in 1949 and Boston in 1950, and of those six thought we probably ought to keep up the alternating plan. However, the significant thing was that thirteen of the Board said they would favor New York in 1949 and Boston in 1950, regardless of any alternating principle. They felt it not unfavorable for the College to meet twice as close together as New York and Boston. I think the President-Elect, Dr. Reginald Fitz, should speak about Boston for 1950. We shall be welcome in Boston, in Cleveland or in St. Louis. We might readily be welcome in Baltimore too, but there was so little interest in Baltimore expressed among the Regents that I have removed Baltimore from the list of contenders. Therefore, your consideration of the 1950 meeting place would have to be among Boston, Cleveland and St. Louis.

A new and interesting suggestion came up at this meeting—Dr. George F. Strong can speak on it. One of the newer Fellows, the Professor of Medicine at the University of Toronto, Dr. Ray Fletcher Farquharson, has expressed, through Dr. Strong, Dr. Harold A. Des Brisay, and some others here, an interest in Toronto in having the College come there some time. We have never held a meeting in Toronto; we have not examined their facilities yet, but I believe that the facilities are adequate, and I think it would be very valuable to the College to keep Toronto in mind for some later meeting.

Boston can provide the Mechanics Hall for meeting facilities; I have examined it and it contains adequate meeting rooms, exhibit space and other facilities; it is near the hotels, and while the building is old, it is certainly adequate.

Now in Cleveland and in St. Louis we would have fine Convention Halls. The rental expenses in Boston, using the Mechanics Hall, which is a private hall, would probably be a thousand or two thousand dollars more than at Cleveland or at St. Louis, where the cities for the most part provide the meeting halls. I feel, however, that we should be influenced more by the medical attractions of the cities.

DR. REGINALD FITZ: I have given this considerable thought, and I think the issue really depends on whether we feel it is proper to break away from the long standing tradition of the College to alternate geographically in its meeting places. There is no question about Boston putting on a particularly good show, because our hospital facilities are well integrated and the hospitals have large amphitheatres. I am sure Mechanics Hall would work well. The puzzling problem is, as Mr. Loveland pointed out, we have to think two years ahead, and we have to consider whether it would be wise to deviate from a long standing tradition. If it is, I am sure that Boston would work all right. It is curious that there is so very little expression of favor in keeping up the old tradition. On the other hand, what we want to do is to give everyone a chance to come to the meetings, and I would hate to run the risk of having Fellows not want to come to the east for two successive years, and I would like to hear it discussed.

MR. LOVELAND: Another quite important consideration is that of who would be the General Chairmen in the various cities.

DR. ERNEST H. FALCONER: Mr. President, I would like information. It is my impression that we haven't many members especially active in St. Louis and who are particularly anxious to have the College come there.

PRESIDENT PALMER: Dr. Ralph Kinsella is very active and would do a good job.

DR. A. B. BROWER: Mr. Chairman, I would just like to give you an impression that I have received from a number of Fellows in the middle west, merely for the purpose of conveying that expression of opinion. I know the opinion of a number of Fellows in Ohio, in particular, and the southern parts of Illinois and Indiana, who are a little bit touched about this business of having these things becoming more

regionalized. There are a number who would particularly like the meeting to be held in the middle west in 1950.

DR. HUGH J. MORGAN: I think we must consider the concentration of our membership. My guess is that the geographical distribution of the members is such that we need to have two meetings on the eastern seaboard to one in any other region of the country. Furthermore, I think the College should go where it best would be served in the terms of the Annual Meeting. One can get on an airplane in the morning and be anywhere in the country by the evening. It is absurd to think about the geographical location as a matter of convenience any more. I strongly favor our going to Boston on many accounts, and perhaps the most important being that I am sure we would have a perfectly grand program.

DR. LEROY H. SLOAN: I am in favor of Boston for 1950, but I think the College should also bear in mind the importance of the fact that it does something for a region when the College meets there, and it does something for the College. We should not lose sight of the fact that where we are weak we should become strong, and we can become strong by putting the Annual Sessions there. My own vote was for St. Louis in 1949 and Boston in 1950. Coming from the middle west, I am perfectly satisfied that it be Boston. We do not have to worry particularly about the geographical end of it, but I think after 1950 we ought to be a little careful about where the next succeeding meeting is to be held, so as not to de-emphasize regions.

To bring it to a head, I move that we meet in Boston in 1950.

DR. MORGAN: I second the motion.

. . . The motion was put to a vote and unanimously carried. . . .

DR. GEORGE F. STRONG: I hope the Regents will keep in mind this possibility of meeting in Toronto. It appeals to me as being properly classified as middle west. The College is not as strong in Canada, and particularly in Ontario, as it should be, and I know that a meeting there would do a great deal to build the prestige of the College, and I believe they could put on a good meeting. I hope that in 1951, or not later than 1952, we may look forward to a meeting there, provided the facilities are adequate.

PRESIDENT PALMER: With the increase in the size of our membership and the increased difficulties in getting larger cities to accommodate us, we might consider at some time the possibility of meeting once in a while at Atlantic City. It would be impracticable, perhaps, to give clinics at Atlantic City. On the other hand, my feeling is that the lectures have been very popular, and it might be possible to increase the lectures and the panels and to omit the clinics once in every so many years.

The next on our agenda is the authorization on behalf of the Regents for the President, General Chairman and the Executive Secretary to complete all necessary arrangements for the 1949 Annual Session.

. . . On motion by Dr. George F. Strong, seconded by Dr. Alex. M. Burgess, and unanimously carried, that authorization was granted. . . .

PRESIDENT PALMER: The Secretary has some communications.

MR. LOVELAND: Dr. William J. Kerr has handed me these two communications, and asked me to read both of them. They originate in the office of Mr. Daniel M. Wilkes, who was the publicist for our Committee on Publicity for this meeting. They have done a most excellent job, and they have included in these letters recommendations and statements concerning their experience.

. . . The Secretary then read the above mentioned communications. . . .

. . . On the motion of Dr. George F. Strong, seconded by Dr. Charles F. Tenney and others, and enthusiastically carried, the Board of Regents extended a special vote of appreciation to Dr. William J. Kerr and Dr. Ernest H. Falconer, General Co-Chairmen, for the very successful meeting in San Francisco. . . .

Adjournment.

Attest: E. R. LOVELAND,  
*Executive Secretary*



# AMERICAN COLLEGE OF PHYSICIANS, INC.

Balance Sheet, December 31, 1947

## GENERAL FUND

Assets		Liabilities	
Current:		Current:	
Cash in Banks and on Hand.....	\$ 74,749.36	Accounts Payable.....	\$ 439.30
Accounts Receivable:		Building Reserve Fund.....	34,723.00
Drexel & Co.....	\$ 1,634.30	Deferred Income:	
Advertising.....	2,321.64	Advance Subscriptions, ANNALS OF INTERNAL MEDICINE, Vols. XXVIII to XXXVI.....	31,263.21
Postgraduate Courses.....	420.00	Restricted Funds:	
ANNALS Excess Illustrations.....	167.86	Chicago Postgraduate Fund.....	\$ 443.30
American Air Lines.....	700.37	Philadelphia Postgraduate Fund.....	2,284.30
		Building Alterations Fund.....	94.60
Inventory of Keys, Pledges and Frames, at Cost.....	477.55	Reserve—Fellowship Fund.....	19,016.69
Accrued Income on Endowment Fund Investments.....	1,521.64	Total Current Liabilities and Funds.....	\$ 88,264.40
Accrued Income on General Fund Investments.....	688.13	General Fund, as annexed.....	270,570.82
Investments at Book Value.....	156,076.42		
Insurance Deposit.....	555.00		
Total Current Assets.....	\$239,312.27		

<b>Deferred:</b>	
Expenses, 29th Annual Session.....	\$ 5,171.02
Advertising, Vol. XXVIII.....	7.46
	5,178.48

<b>Fixed:</b>	
College Headquarters:	
Real Estate.....	57,728.45
Less Depreciation.....	11,000.00
	46,728.45
New Building Appropriation.....	55,000.00
Furniture and Equipment, at Cost.....	14,596.75
Less Depreciation.....	11,151.23
	3,445.52
Investment, Real Estate, 404-12 S. 42nd Street.....	9,170.50
	9,170.50
	\$358,835.22

ENDOWMENT FUND	
Cash in Banks:	
General.....	\$1,996.78
A. B. Brower Fund.....	2,500.00
	\$ 4,496.78
Accrued Income on Investments.....	1,521.64
Investments at Book Value:	
General.....	256,788.11
James D. Bruce Fund.....	10,000.00
	266,788.11
(TOTAL ASSETS, \$631,641.75).....	\$272,806.53
Endowment Fund, Principal:	
General.....	\$258,784.89
James D. Bruce Fund.....	10,000.00
A. B. Brower Fund.....	2,500.00
	\$271,284.89
Accrued Income, Due to General Fund.....	1,521.64
(TOTAL LIABILITIES AND FUNDS, \$631,641.75).....	\$272,806.53

*Operating Statement*

## GENERAL FUND

*For the Year Ended December 31, 1947*

Balance, January 1, 1947.....			\$234,159.26
Less:			
Transfer to Endowment Fund of the Initiation Fees of Life Members.....	\$ 6,920.00		
Adjustment of Dec., 1946, Advertising.....	2.16		
Transfer from 1946 Chicago Regional Meeting Surplus.....	191.62		
Transfer from 1946 ANNALS OF INTERNAL MEDICINE Subscription Overpayment.....	3.00	7,116.78	\$227,042.48
Net Income for the Year Ended December 31, 1947, as Annexed.....			43,528.34
BALANCE, December 31, 1947.....			<u>\$270,570.82</u>

## ENDOWMENT FUND

*For the Year Ended December 31, 1947*

Principal Account, January 1, 1947.....			\$223,373.89
Add:			
Life Membership Fees received during 1947.....	\$28,306.67		
Transfer of Initiation Fees of New Life Members from General Fund.....	6,920.00		
Transfer from Dues Account.....	70.33		
Transfer from Subscription Account.....	18.00		
Transfer from Initiation Fees Account.....	80.00		
Net Profit on Endowment Fund Investments.....	16.00	35,411.00	\$258,784.89
JAMES D. BRUCE FUND:			
Principal, January 1, 1947 (no changes).....			10,000.00
(Income included in General Fund Statement for 1947)			
A. B. BROWER FUND:			
Principal Received.....			2,500.00
TOTAL, Endowment Funds.....			<u>\$271,284.89</u>
TOTAL, All Funds.....			<u>\$541,855.71</u>

*Summary of Operations for the Calendar Year 1947**Income:*

Annual Dues.....		\$ 53,516.25	
Initiation Fees.....		15,538.67	
Subscriptions, ANNALS OF INTERNAL MEDICINE.....		62,435.59	
Advertising, ANNALS OF INTERNAL MEDICINE.....		26,246.07	
Income from Investments, General Fund (including Accrued) ..		7,327.29	
Income from Investments, Endowment Fund (including Accrued)		8,784.21	
Dividend on Perpetual Insurance Deposit.....		60.00	
Sale of 1947 Membership Roster.....		25.25	
Postgraduate Courses, Balance.....		1,490.19	
Rent—404-12 S. 42nd Street.....		\$ 1,649.54	
Less: Maintenance.....	\$ 303.42		
Light, Gas and Water.....	32.78		
Taxes.....	489.55		
Insurance (fire).....	20.00		
Insurance.....	32.76	878.51	771.03

Profit from Sales of General Fund Securities.....	86.40	
Profit on Equipment Traded in.....	34.70	
Twenty-eighth Annual Session:		
Exhibits.....	\$16,384.21	
Guest Fees.....	1,767.00	
Banquet Balance.....	200.49	18,351.70
<b>TOTAL INCOME.....</b>		<b>\$194,667.35</b>

*Expenses:*

Salaries.....		39,652.17
Communications.....		6,114.82
Office Supplies and Stationery.....		3,417.84
Printing.....		40,438.87
Traveling Expenses (exclusive of Annual Session).....		2,389.43
Maintenance, Executive Secretary's Office.....		34.44
Miscellaneous.....		2,037.73
Research Fellowships.....		20,000.00
College Headquarters:		
Maintenance.....	\$ 3,932.99	
Heat, Light, Gas and Water.....	1,072.25	
Insurance.....	89.93	
Taxes.....	170.77	5,265.94
Depreciation on Building.....		1,000.00
Depreciation on Furniture and Equipment.....		607.86
Keys, Pledges and Frames.....		163.24
John Phillips Memorial Prize.....		252.46
Twenty-eighth Annual Session:		
Publicity Committee.....	\$ 516.00	
Ladies' Entertainment Committee.....	1,001.24	
"Harvey," Harris Theater.....	510.25	
Convocation.....	926.61	
Governors'-Regents' Dinner.....	518.24	
Salaries.....	7,119.66	
Communications.....	747.45	
Office Supplies and Stationery.....	201.72	
Printing.....	3,186.85	
Traveling Expenses.....	5,740.54	
Miscellaneous.....	3,018.99	23,487.55
Investment Counsel Service.....		250.00
Security Custodian's Fee.....		398.00
Employees' Pension Fund.....		2,254.77
Collection and Exchange.....		372.14
1947 Supplement.....		767.96
Regional Meetings.....		2,233.79
<b>TOTAL EXPENSES.....</b>		<b>\$151,139.01</b>

Net Income for 1947 Credited to General Fund..... \$ 43,528.34

These financial data taken from the official Auditor's Report.

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 29

AUGUST 1948

NUMBER 2

---

## STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS \*

By J. BURNS AMBERSON, F.A.C.P., and WILLIAM H. STEARNS,  
*New York, N. Y.*

THE effects of streptomycin administered to tuberculous patients have been shown to be strikingly beneficial in some phases of the disease, equivocal in some, and quite insignificant in others. Toxic damage by the antibiotic has been a frequent occurrence but this can be minimized by limiting the dose and the length of treatment. A more serious disadvantage, insurmountable thus far, is the development of bacterial resistance to streptomycin which often nullifies its further therapeutic action. While its potency against tuberculosis is unprecedented by any other drug, there are already some manifest limitations of its effectiveness. It has not altered the fundamental character of the disease to yield but stubbornly to treatment; nor that other subtle quality of seeming to yield for a time, only to relapse with renewed destructiveness. An important task, therefore, is to learn more of the limitations, which as yet are not precisely defined, so that streptomycin may be employed with maximum benefit at a critical point in the course of the disease.

A good many years are always required to determine the place of any treatment for tuberculosis, and streptomycin is no exception. Considering the short time since Waksman and his associates<sup>1</sup> announced their discovery and since Feldman and Hinshaw<sup>2</sup> demonstrated its therapeutic effects against tuberculosis, it is remarkable that so much knowledge of the drug has accumulated. This is in part due to the coöperative efforts of numerous investigators, hospitals and private and public agencies, including particularly the manufacturers of streptomycin, the American Trudeau Society, the Veterans Administration, and the National Institute of Health of the United States Public Health Service.

The purpose of this paper is to suggest some clinical interpretations which, although somewhat tentative, seem reasonable at this time. These

---

\* Presented at the San Francisco meeting of the American College of Physicians, April 22, 1948.

From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Chest Service of Bellevue Hospital.

are based on some knowledge of the work of others, particularly that of McDermott and Muschenheim<sup>3</sup> at the New York Hospital, and on two studies in which the authors are now participating, one in the Chest Service of Bellevue Hospital,\* and the other in the Chest Section of the Medical Service of the Bronx Veterans Hospital.† The former is devoted mainly to an investigation of the effects of streptomycin in acute forms of tuberculosis (treatment has been completed thus far in 40 cases) while the latter is restricted to genitourinary tuberculosis (treatment completed in 25 cases). These studies will be reported in detail later. In addition, we have had experience with the drug in these hospitals, outside of the organized studies, in the routine care of patients.

In dealing with a disease as variable in its clinical manifestations as tuberculosis, it is not possible with precision to distinguish changes which occur in its natural evolution from those influenced by treatment; this is particularly true after the disease has become chronic. It was partly for this reason that we chose to study streptomycin in some cases of relatively early and severe acute disease. It is not always easy to evaluate the effects of streptomycin even in these, but at least some of the confusion met in more chronic cases that present both destructive and reparative lesions is avoided.

*Symptomatic Response.* When streptomycin exerts its maximum effect, patients suffering from acute febrile tuberculosis often experience a decided subjective change within three or four days, manifested by a feeling of well being and a return of energy and strength. This may antedate the subsidence of fever and may be associated with an improvement of appetite and the loss of other subjective evidences of toxemia. In a few cases high fever subsides abruptly, almost by crisis, within a week after treatment is started but in most there is a more gradual defervescence; this, however, is at a distinctly more steady and rapid rate than is usually observed under rest treatment alone. These patients, if previously malnourished and depleted, then may gain weight and, in the space of a few months, acquire an outwardly healthy, well nourished appearance. Nevertheless, a more sensitive indicator of toxemia, such as the erythrocyte sedimentation rate, may remain accelerated for several months after the disappearance of subjective symptoms.

The effect on local symptoms likewise is sometimes quite pronounced. Tuberculous laryngitis, causing severe pain and dysphagia, may respond so quickly that the patient is able to eat with little or no discomfort within several days to a week. Cough and expectoration often subside rapidly. In genitourinary cases there may be partial or complete relief of frequency, dysuria and other symptoms of bladder irritability. Such effects may be

\* Supported by a contribution of streptomycin under the Streptomycin Manufacturers-American Trudeau Society Program, and by grants from the National Tuberculosis Association and the National Institute of Health.

† In coöperation with the Veterans Administration Streptomycin Committee. The urological observations were made by Dr. John K. Lattimer.

observed, of course, in the standard conservative treatment of tuberculosis, but under streptomycin therapy they are often more prompt and consistent.

*Effect on Lesions.* Relief from constitutional symptoms, such as fever, and sometimes also from local symptoms, usually occurs before any change in local lesions can be demonstrated; thus, the early cessation of the pain of tuberculous laryngitis may antedate any visible change in the appearance of the larynx. Presumably this is due to the retardation or arrest of active inflammatory edema, thus lowering the tension in the tissues and easing the irritation of sensory nerves. Within a few days to one or two weeks, if deep destruction has not already occurred, edema and redness of the laryngeal tissues may diminish, shallow ulcers may be seen to regress and in time the structures may assume a superficially normal appearance. Similarly, gross tuberculous inflammatory changes in the mucosa of the bladder may be observed cystoscopically to diminish, while its capacity increases toward normal. With respect to the lungs, a rather common manifestation of subsiding inflammation is the decrease of the purulence and daily output of sputum, while serial roentgenograms, taken at intervals of a few days to several weeks, often show rapid clearing of soft mottled shadows indicative of resolution.

This checking of active tuberculous inflammation and subsequent resolution of the inflammatory exudate is observed most strikingly in acute cases. When the response to streptomycin is prompt the rate of resolution is often definitely accelerated over that which would be expected under good rest treatment alone. When the duration of tuberculous pneumonia is only three or four weeks and a prompt arrest of the inflammatory process is induced by streptomycin, the subsequent resolution sometimes seems to be almost complete. The factor responsible for the resolution appears to be the suppressive effect of the antibiotic on bacterial growth before caseous necrosis has occurred.

Under rest treatment alone the tempo is slower, and caseation, therefore, is usually more extensive. However, the conclusion that complete resolution has occurred may be erroneous since we know that minute caseous foci may persist, invisible by roentgen-ray; sometimes the latter are betrayed by the persistence of fine râles after the roentgenogram shows virtually complete clearing.

In a number of cases of early tuberculous pneumonia there has been a prompt symptomatic response to the administration of streptomycin but a considerable lag in the resolution of the lesions; this proceeded then to a striking degree during two or three or more months after the completion of the streptomycin course. It is apparent, therefore, that the failure of lesions to resolve promptly is not necessarily an indication to continue the administration of the drug beyond the allotted time.

*Lesions not Affected by Streptomycin.* So far as the morphology of the lesion is concerned, we have learned that the extent of caseous necrosis,

which in turn depends upon the type and duration of the inflammation, limits to a great degree the response to streptomycin. Severe tuberculous pneumonia of two or three months' duration is usually widely caseous; there may be a temporary symptomatic response but with little or no demonstrable evidence of resolution and, in such instances, early relapse is probably to be expected. The same is true of caseous lesions in other sites. Tuberculous abscesses in soft tissues may persist as such. Nodular, presumably caseous, lesions in the epididymis and prostate usually do not show any striking change. This is not surprising in view of our fundamental knowledge that caseous lesions are organized slowly, with or without sloughing or ulceration. To what extent such healing is favored and accelerated after the use of streptomycin remains to be determined by some years of observation.

The presence of caseous lesions goes far to explain many observed phenomena. The frequent relapse and fatal course of tuberculous meningitis after an initial striking response to streptomycin therapy seems in some cases to be explained by the presence of caseous lesions in the cortex of the brain, which are the sources of renewed invasion of the meninges some time after the drug has had its effect. Similarly, streptomycin may promote temporary clinical recovery from generalized miliary tuberculosis and resolution of numerous non-necrotic metastatic lesions while the caseous focus of origin, perhaps invisible, remains little affected and may at a later date seed the blood stream again with a fatal result. In pulmonary cases, renewed progression of the disease by bronchogenic dissemination is more often related to persistent caseous foci containing viable tubercle bacilli than to any other single factor. Unless these residual necrotic lesions can be held in abeyance by prolonged and careful rest treatment to allow for the slow process of fibrous organization, relapse is almost inevitable.

However impressive may be the immediate effects of streptomycin, there is as yet no reason to think that the time required for the ultimate healing of residual caseous lesions and lasting clinical recovery is shortened; in fact, it may of necessity be lengthened. For example, initial recovery under streptomycin from acute progressive tuberculous pneumonia should be regarded only as a respite for the patient whose natural resistance failed to cope with the infection; a favorable balance can be restored but slowly, if at all. He should have perhaps a year or more of bed rest, and another year or so of convalescent care in order, as far as possible, to promote permanent recovery.

Caseous necrosis, as a rule, is not as deep and massive in canalicular structures such as the larynx, bronchi, intestine and bladder, as it is in visceral tissues. Logically, therefore, it might be supposed that tuberculosis in the former would be more accessible to the action of streptomycin, and this seems to be borne out by the observations. The prompt improvement of lesions here, as well as in the skin, is on the average more striking than it is in deeply involved viscera such as the lungs or the kidneys.

Even though ulcerated caseous lesions are sometimes affected little, if at all, by streptomycin, the exudation and discharge from them may be at

least temporarily diminished, as indicated, for instance, by an improvement in the amount and character of the sputum or in the degree of pyuria. Such changes are frequently observed without any appreciable difference in the size of the pulmonary cavity or the renal defect. Nevertheless, even a partial control of purulent exudation may be a desirable thing, particularly to help avoid further dissemination of the infection through the bronchi in the case of the lung, or through the ureters in the case of the kidneys. This may help prepare the way for other needed treatment such as artificial pneumothorax or surgical intervention. On the other hand, the disappearance of tubercle bacilli from the sputum or the urine may be misleading, since this is not good evidence of healing unless there is also a simultaneous obliteration of the ulcerated lesions from which the organisms were discharged.

In several cases of tuberculous pneumonia we have observed the lesions to break down and excavate rapidly during the course of streptomycin treatment. In spite of this, new bronchogenic lesions were not demonstrated. Here, it would seem, we observe in a patient with poor native resistance a temporary prevention of new inflammation without any control of older necrotic foci.

*The Importance of Vital Resistance.* Almost all who have studied the effects of streptomycin recognize the importance of vital resistance in the final issue of the case. It is well known that the identification of the factors involved is uncertain and relatively crude. We appreciate the relationships of age, sex, race, and state of nutrition, but beyond this we are obliged to rely only upon judgments which often are much more intuitive than scientific. Brief experience, however, seems rather clearly to indicate that relapse after streptomycin treatment is relatively more frequent in those with poor native resistance and that this occurs earlier and with greater severity. The implication is clear, therefore, that in such cases facilities should be available for long and rigid rest treatment, perhaps aided by collapse therapy, in order to gain the most from any temporary benefit of the drug.

*Drug Resistance.* As Muschenheim has reasoned, it would be desirable theoretically to administer a drug like streptomycin during many months to obtain lasting benefits from its antimicrobial effects. This would be obligatory were it not for the development of drug resistance among tubercle bacilli.

The studies of Steenken,<sup>1</sup> McDermott,<sup>2</sup> Youmans,<sup>3</sup> and others have shown that resistant variants of the bacillus are recognized in cultures of sputum or other exudates within four weeks of the start of treatment and that such resistance becomes more frequent the longer treatment is continued; after three to four months 70 per cent or more of the patients harbor bacilli with resistance so strong that the usual therapeutic doses of the drug are no longer effective. The development of resistance seems to be more closely related to the duration of treatment than to the daily dose employed. Cumulative evidence suggests that bacterial resistance, once developed, may well be permanent. In many cases this accounts for the failure of streptomycin



to have any further effect even though the initial benefit may have been striking. However, there is some evidence that strains of varying resistance occur in different lesions in the treated patient and that in such cases a renewed dissemination of sensitive bacilli may be controlled by retreatment with streptomycin. Because of these observations a number of studies are under way to determine the optimum dosage of the drug and the optimum time of administration. Our own investigation of 40 cases of acute tuberculosis, 18 treated with 2 grams of streptomycin daily, and 22 with 1 gram daily for 42 days, indicates that this relatively short period may be as effective in some instances as a longer period of administration. In these regimens, development of drug resistant variants is approximately 25 to 30 per cent, including a number of cases in which drug resistance has continued to increase after the termination of treatment. Such a regimen, therefore, provides a possible therapeutic leeway for retreatment should the first course of the drug prove to be inadequate. It also has the advantage that patients who, after a period of rest cure, require surgical intervention for the tuberculosis, may then expect some protection and benefit under a renewed course of streptomycin.

*Toxicity of Streptomycin.* The toxic effects of the drug in human beings have been described by Farrington et al.<sup>9</sup> The damage of the labyrinthine apparatus is the most common and serious when the drug is administered in high dosage for long periods of time. Our study of relatively smaller doses for six weeks indicates that 1 gram of the drug a day does not destroy vestibular function, as shown by caloric tests, although there may be occasional partial impairment. By contrast, 2 grams daily for the same period has caused complete loss of function in 12 of the 18 cases treated. The damage is persistent and presumably permanent, although the patient may be able to compensate. It should be emphasized that complete loss of this function, as determined by caloric tests, may occur although the patient may experience no vertigo or other symptoms so long as he remains in bed.

*Schedule of Treatment.* Because of possible toxic effects of streptomycin and the high incidence of drug fastness after three to four months of treatment, an effort has been made to obtain the therapeutic effects with 1 to 2 grams of the drug daily for six weeks. In acute pneumonic cases 1 gram seems to us to be as effective as 2 grams. More study will be required to determine the optimum regimen which will probably vary from case to case. It seems important not to exhaust the effectiveness of the drug during the initial course of treatment unless the indications are very urgent.

In desperate cases of tuberculosis such as generalized hematogenous miliary tuberculosis and tuberculous meningitis, where the termination under ordinary conditions is usually fatal in a few weeks or several months, we are in agreement with many others that the disadvantages of drug toxicity and bacterial resistance should be ignored and that streptomycin should be administered intramuscularly in daily doses totalling 40 mg. per kg. body weight (2 gm./110 pounds) for a period of 40 days. In addition, in menin-

gitis, 50 mg. should be given intrathecally at 24 to 72 hour intervals during the 90 days. In most cases there will be at least a temporary remission of the disease although relapses occur at a rate which, in the case of meningitis, is exceedingly high; i.e., approximately 80 per cent fatality. In these situations, the reports of Lincoln and her associates<sup>7</sup> suggest that the addition of promizole may be beneficial. The place of the sulfones, para-aminosalicylic acid and other agents, as supplements to streptomycin, can be established only by further investigation.

In cases of acute tuberculous pneumonia known to be of short duration (two to four weeks) benefit can usually be expected with 1 gram of streptomycin, intramuscularly, daily for a course of six weeks. If, after a short interval, the symptoms recur and the disease progresses, retreatment is sometimes effective. If the tuberculous pneumonia is of longer duration and presumably extensively caseous, a longer period of continuous treatment is probably justified, although it is questionable whether larger doses will prove to be more effective. In these cases the incidence of relapse can be expected to be high and eventually no further effect can be anticipated from streptomycin.

In milder cases, if streptomycin seems indicated at all, there is strong reason to use small doses for relatively short periods of time. This should probably not exceed 1 gram a day for six weeks and in many cases the course could well be terminated earlier than six weeks if the desired effect is being approached. Such a regimen may achieve limited goals such as the improvement of a bronchial lesion or the closure of a cutaneous sinus. In every case, a careful evaluation of the situation should be made particularly to prognosticate whether more critical episodes might arise in the future. If so, it may be wise to withhold streptomycin; in other words, use light arms for minor engagements and save the heavy artillery for the crucial battles ahead. For the reasons stated, it is generally agreed that patients who may be expected to respond to conventional rest treatment should not be treated with streptomycin even though this might accelerate early symptomatic improvement.

#### DEDUCTIONS

Until more experience accumulates, any deductions must be qualified. At the moment, however, the following interpretations of some of the evidence seem reasonable:

The effects of streptomycin in tuberculosis are most evident in promoting the control of acute inflammatory changes, presumably by the arrest of bacterial activity. In recent lesions of this character, the effect may be prompt and striking and may help to avoid extensive caseous necrosis, may relieve the heavy demands on the patient's vital resistance and may provide a respite during which the natural processes of healing may be initiated. A continuation of rest treatment is necessary then to further the healing which, at best, is very slow.

The early favorable effects of streptomycin in acute disease may be of short duration because of low native resistance, extensive caseous necrosis and the development of bacterial resistance against the drug. Relapse will probably be more frequent in such cases responding to streptomycin than in acute cases which respond favorably to rest treatment alone.

In chronic tuberculosis streptomycin may be used for limited and well defined purposes but it should not be administered to the point of ineffectiveness for relatively trivial episodes.

Streptomycin should be administered for a prolonged time, regardless of anticipated toxic effects and bacterial resistance, in desperate forms of the disease, detected early; i.e., acute generalized hematogenous tuberculosis and tuberculous meningitis.

In less urgent situations, the length of the course of treatment and the daily dose of the drug should be limited if this seems likely to be adequate.

Phases of tuberculosis which may be expected, according to experience, to respond well to good rest treatment should not be treated with streptomycin.

In any case a careful and complete evaluation of the actual and potential status of the disease should be made to determine the wisdom of administering streptomycin, holding it in reserve, or relying wholly on conventional rest treatment.

#### BIBLIOGRAPHY

1. SCHATZ, A., BUGIE, E., and WAKSMAN, S. A.: Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria, *Proc. Soc. Exper. Biol. and Med.*, 1944, *lv*, 66-69.
2. FELDMAN, W. H., and HINSHAW, H. C.: Effects of streptomycin on experimental tuberculosis in guinea pigs: A preliminary report, *Proc. Staff Meet., Mayo Clinic*, 1944, *xix*, 593-599.  
HINSHAW, H. C., and FELDMAN, W. H.: Streptomycin in treatment of clinical tuberculosis: A preliminary report, *ibid.*, 1945, *xx*, 313-318.
3. McDERMOTT, W., MUSCHENHEIM, C., HADLEY, S. J., BUNN, P. A., and GORMAN, R. V.: Streptomycin in the treatment of tuberculosis in humans. I. Meningitis and generalized hematogenous tuberculosis, *Ann. Int. Med.*, 1947, *xxvii*, 769-822.  
MUSCHENHEIM, C., McDERMOTT, W., HADLEY, S. J., HULL-SMITH, H., and TRACY, A., *ibid.*, 989-1027.
4. STEENKEN, W.: Minutes of the fourth streptomycin conference, Veterans Administration, Oct. 9-12, 1947, St. Louis, p. 52.
5. YOUMANS, G. P., and KARLSON, A. G.: Streptomycin sensitivity of tubercle bacilli, *Am. Rev. Tuberc.*, 1947, *lv*, 529-535.  
WILLISTON, E. H., and YOUMANS, G. P.: Streptomycin resistant strains of tubercle bacilli, *ibid.*, 536-539.
6. FARRINGTON, R. F., HULL-SMITH, H., BUNN, P. A., and McDERMOTT, W.: Streptomycin toxicity, *Jr. Am. Med. Assoc.*, 1947, *cxxxiv*, 1-29.
7. LINCOLN, E. M., KIRKSE, T. W., and DeVITO, E.: Tuberculous meningitis in children. A preliminary report of its treatment with streptomycin and "promizole," *Jr. Am. Med. Assoc.*, 1948, *cxxxvi*, 593-597.

# THE URINARY EXCRETION OF RADIOACTIVE IODINE AS AN AID IN THE DIAGNOSIS OF HYPERTHYROIDISM \*

By JANET W. McARTHUR, M.D.,<sup>†</sup> RULON W. RAWSON, M.D., REX G. FLUHARTY, and J. H. MEANS, M.D., F.A.C.P.,  
*Cambridge, Massachusetts*

THYROTOXICOSIS, in its classical form, is one of the most readily recognizable of all the diseases in medicine. In atypical form, however, hyperthyroidism may present formidable diagnostic difficulties. A growing number of laboratory aids have been devised to reduce the number of undiagnosed borderline cases, characterized by nervousness combined with a persistently elevated metabolic rate, which plague every thyroid clinic.

Among these auxiliary diagnostic technics is the so-called "iodine tolerance test," designed to appraise the functional activity of the thyroid gland by measurement of its capacity to take up iodine. Experimental precedent for this test derives from the classic perfusion experiments of Marine and his associates<sup>1, 2</sup> who demonstrated the selective affinity of the thyroid gland for iodine. Hyperplastic glands, with a low iodine content, were shown to remove the largest quantities of iodine from the perfusion fluid.

Clinical determination of iodine tolerance has been attempted in a number of ways: (a) Measurement of the rate and completeness of disappearance from the blood stream of a calculated amount of iodine administered to the patient.<sup>3, 4, 5, 6, 7</sup> The blood iodine curve of the thyrotoxic patient whose thyroid is avid for iodine does not show the peak which characterizes the curve of the normal or non-toxic goitrous individual; the whole curve lies below the arbitrary limit of normal. A disadvantage to this technic is that it requires multiple determinations of the level of blood iodine, an intricate laboratory procedure. (b) Direct determination of the uptake of radioactive iodine by external gamma ray measurements on the thyroid in situ with the Geiger-Müller counter.<sup>8, 9</sup> By this method, certain patients with classic Graves' disease appeared to be distinguishable from patients with hyperophthalmopathic Graves' disease and from normal individuals by their greater uptake of labelled iodine. The error in this type of measurement is in all likelihood appreciable, owing to individual variations in the size and anatomical position of the thyroid and, during the initial phases, to the background of radioactivity in the patient's body. (c) Quantitation of the iodine excreted in the urine during a given period of time after the administration

\* Received for publication August 18, 1947.

From the Thyroid Clinic of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School and the Radioactivity Center of the Department of Physics of the Massachusetts Institute of Technology.

<sup>†</sup> Henry P. Walcott Fellow.

Aided by grants-in-aid from the Committee on Growth, American Cancer Society, Parke Davis & Company, the H. N. C. Gift Fund, Harvard University, and an anonymous donor.

of a standard dose of iodine. Chemical methods for determining the urinary iodine excretion have been employed for this purpose by Elmer,<sup>10</sup> Watson<sup>4, 5</sup> and by Perkin, Brown and Lang.<sup>3</sup> Disadvantages of this technic are the difficulty of the analytical procedure and insensitivity of the method due to the fluctuant level of excretion of dietary iodine and the consequent necessity for administration of a relatively large test dose of iodine.

The precision and ease with which the urinary excretion of iodine can be determined has been greatly enhanced by the introduction of the radioactive isotopes of iodine. Moreover, a dynamic conception of iodine metabolism can be gained since the iodine administered in the test dose becomes distinguishable from iodine already present in the body. Physical methods

TABLE I  
The Urinary Excretion of Iodine Administered to Euthyroid and Hyperthyroid  
Individuals as Reported by Various Investigators

Author	Dose of Iodine	Route	Urinary Iodine Excretion				
			No. of Patients	Type of Patients	Average	Range	Period of Urine Collection
Elmer <sup>10</sup>	1300 gamma	Intra-venous	19	Euthyroid	16.6%	11.7-20.5%	6h
			9	Hyperthyroid	15.6%	0.8-24 %	
			3	Severe		0.8-24	
			6	Mild		14.0-21	
Hertz and Roberts <sup>8</sup>	<2 mg. Labelled with radio-active iodine	Oral	1	Euthyroid	63.0%	10.0-37 %	72h
			6	Hyperthyroid	25.0%		
			6	Ophthalmopathic Graves' disease	46.0%		
Watson <sup>5</sup>	250 gamma/kilo	Intra-venous	24	Euthyroid	552 gamma	44-1396 gamma	6h
			27	Hyperthyroid	403	30-1734	
Hamilton and Soley <sup>9</sup>	14 mg. Labelled with radio-active iodine	Oral	6	Euthyroid	83.5%	76.0-88 %	5d
			1	Hyperthyroid (toxic nodular goiter)	84.6%		
Perkin, Brown, Lang <sup>3</sup>	75 mg.	Oral	7	Euthyroid	20.6%	10.3-25.7%	24h
			9	Hyperthyroid	12.8%	4.2-15.5%	

for measuring the urinary excretion of radioactive iodine have been utilized in a small group of patients by Hertz and Roberts.<sup>8</sup> A possible objection to the radioactive tracer method is that the presence of the radiation may alter the physiological properties of the tissues under investigation. While this contingency seems unlikely in view of the great dilution of the radioactive element, experimental study directed toward resolution of the difficulty is in progress in this laboratory.

In table 1 is summarized the urinary excretion of iodine administered to euthyroid individuals and to patients with untreated hyperthyroidism, as

reported by the various investigators cited above, together with the dose of iodine employed and the route of administration. These data have seemed to us sufficiently promising to warrant further investigation. We have attempted to evaluate the clinical usefulness of the measurement of radioactive iodine excretion by defining more precisely the range of excretion to be anticipated in non-thyrotoxic individuals and in patients with hyperthyroidism.

TABLE II

Clinical, Metabolic and Radioactive Iodine Excretion Data for the Non-Thyrotoxic Group  
A. Patients initially suspected of having Graves' disease

Case No.	Complicating Diseases	Extent of Thyroid Enlargement	48 Hour RaI Excretion (%)	Activity of Tracer (Micro-curies)	Dose of Iodide (gamma)	B.M.R.
1	Pregnancy	$1\frac{1}{2} \times N$ size	36	100	2.4	+11
2	Arteriosclerotic heart disease	—	44	100	2.0	+20
3	Nodular goiter	$2 \times N$ size	85	100	5.0	+7
4	Nodular goiter	$2 \times N$ size	54	100	3.3	+3
5	—	—	38	100	8.0	+8
6	Anxiety neurosis	—	71	200	100.0	+2
7	Alcoholism, chronic hepatitis	—	43	100	5.5	+22
8	Chronic rheumatic heart disease	$2 \times N$ size	92	100	4.0	+18
9	Hypertensive cardiovascular disease, nodular goiter	$2 \times N$ size	52	100	2.4	+5
10	Hypertensive cardiovascular disease, Parkinsonism	—	56	100	4.0	+32
11	Bronchial asthma	—	36	100	3.2	+26
12	Nodular goiter	$1\frac{1}{2} \times N$ size	32	100	5.0	+7
13	Hypertensive cardiovascular disease, anxiety neurosis	$1\frac{1}{2} \times N$ size	50	100	3.2	+2
14	Pheochromocytoma	—	40	100	40.0	+65
15	Thyrotoxicosis factitia	—	98	300	100.0	+52
16	Hypertensive cardiovascular disease	$1\frac{1}{2} \times N$ size	89	100	100.0	+37
17	Obstructive jaundice, nodular goiter	$2 \times N$ size	43	50	50.0	+28
18	Hypertensive cardiovascular disease	—	98	100	100.0	+20

B. Patients given radioactive iodine for other research purposes

19	Chronic lymphatic leukemia	—	50	100.0	10.0	+7
20	Acute lymphatic leukemia	—	53	100.0	10.0	—
21	Chronic lymphatic leukemia	—	59	100.0	60.0	+2
22	Metastatic carcinoma cervical nodes	—	76	100.0	34.0	—
23	Fetal adenoma of thyroid	Single nodule	38	1000.0	60.0	-4
24	Struma nodosa and papillary adenocystoma of thyroid	Single nodule	58	2000.0	200.0	+2
25	Papillary adenocystoma of thyroid	Single nodule	83	1000.0	34.0	—
26	Struma nodosa of thyroid	Single nodule	63	1000.0	160.0	0
27	Hurthle cell tumor of thyroid, benign	Single nodule	51	1000.0	54.0	-7
28	Colloid adenoma of thyroid	Single nodule	65	1000.0	100.0	-9
29	Papillary carcinoma of thyroid	Single nodule	71	1000.0	100.0	-1
30	Papillary carcinoma of thyroid	Single nodule	74	800.0	16.0	-19

## METHODS AND MATERIALS

Tracer doses (2 to 160 gamma) of sodium iodide labelled with radioactive iodine ( $I^{131}$ ) whose specific activity varied from 50 to 2000 microcuries (in the majority of instances the activity was 100 microcuries) were administered orally to patients. Urines were collected for 48 hours following the administration of the labelled iodine, and the percentage excretion determined from the specific activity of an aliquot. A number of seemingly toxic patients had no palpable goiter. To these individuals a dose of radioactive iodine was administered and the entire body searched for iodine-concentrating tissue 24 to 36 hours later with the Geiger counter.

The non-thyrotoxic group comprised 30 cases. Of these, 18 were initially suspected of having hyperthyroidism. The diagnosis of thyrotoxicosis was finally excluded in these patients after prolonged study and observation.

TABLE III

Clinical, Metabolic and Radioactive Iodine Excretion Data for the Thyrotoxic Group

Case No.	Type and Size of Goiter	Complicating Diseases	48 Hour RaI Excretion (%)	Activity of Tracer (Microcuries)	Dose of Iodide (gamma)	B.M.R.
1	Diffuse, $2 \times N$	Hypertensive cardiovascular disease	30	173	5.0	+54
2	Diffuse, $3 \times N$	—	39	100	10.0	+22
3	Diffuse, $1\frac{1}{2} \times N$	Duodenal ulcer, ovarian tumor	21	300	100.0	+23
4	Not palpable	—	30	184	8.6	+23
5	Diffuse, $2 \times N$	Thyrotoxic myopathy	18	100	32.0	+60
6	Diffuse, $3 \times N$	—	15	100	15.0	+42
7	Diffuse, $2\frac{1}{2} \times N$	Anxiety neurosis	26	100	100.0	+55
8	Nodular, $2 \times N$	—	38	100	100.0	+25
9	Nodular, $2 \times N$	—	15	100	100.0	+24
10	Diffuse, $2 \times N$	—	19	100	5.5	+20
11	Nodular, $2 \times N$	—	22	1730	44.0	+32
12	Diffuse, $1\frac{1}{2} \times N$	—	8	100	4.5	+61
13	Diffuse, $3\frac{1}{2} \times N$	—	16	250	150.0	+37
14	Diffuse, $2 \times N$	—	31	100	2.4	+13
15*	Diffuse, $2 \times N$	—	23	100	4.0	+27
16*	Nodular, $3 \times N$	—	15	100	150.0	+41
17*	Diffuse, $2 \times N$	—	32	100	100.0	+42
18	Diffuse, $1\frac{1}{2} \times N$	Rheumatoid arthritis	35	100	100.0	+32
19	Nodular, $1\frac{1}{2} \times N$	Rheumatoid arthritis	26	100	100.0	+48
20	Diffuse, $2\frac{1}{2} \times N$	Lung malignancy	7	100	100.0	+55
21	Diffuse, $2 \times N$	Rheumatoid arthritis	38	100	100.0	+46
22	Diffuse, $2 \times N$	—	45	100	100.0	+26

\* Persistent thyrotoxicosis after radioactive iodine therapy.

Eleven were patients with non-metabolic diseases given radioactive iodine for some other research purpose. Table 2 summarizes the diagnoses in these patients, together with the basal metabolic rate, urinary excretion of radioactive iodine, and the iodide content and specific activity of the administered tracer. The last eight patients in the table were individuals operated upon for the removal of a single nodule of the thyroid. Only those cases in whom the tumor tissue was shown to be non-functional by failure to take up radioactive iodine have been included.

The thyrotoxic group consisted of 22 cases of classic untreated \* Graves' disease. Table 3 presents the clinical, metabolic and excretion data for these patients.

### RESULTS

The mean radioactive iodine excretion by the 30 non-thyrotoxic patients was 60 per cent, range 23 per cent to 98 per cent. The mean excretion by the 22 thyrotoxic patients was 25 per cent, range 7 per cent to 45 per cent. The extent of overlapping may be gauged from the histogram (figure 1).

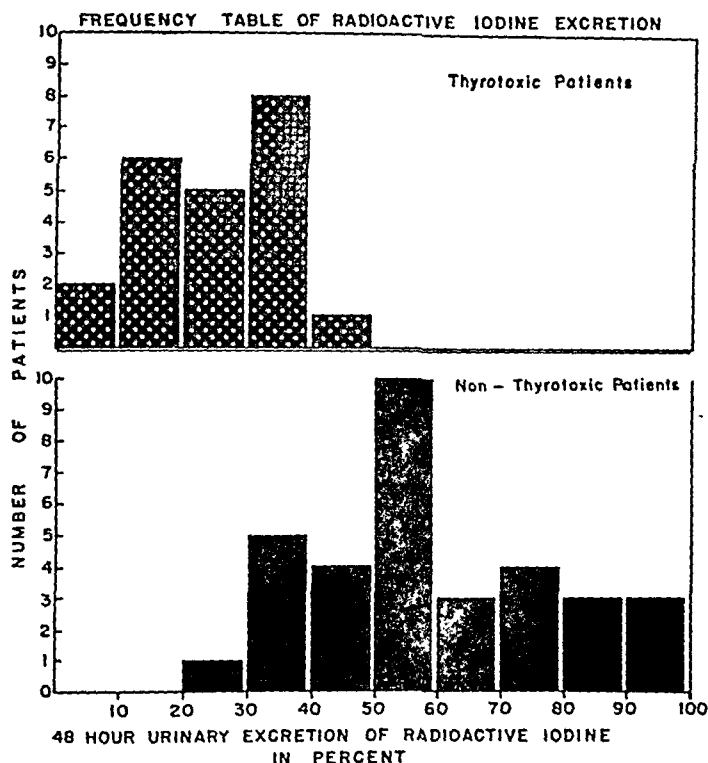


FIG. 1. The histogram showing frequency distribution of 48 hour urinary excretion of radioactive iodine in per cent in thyrotoxic and non-thyrotoxic patients.

As shown by the scatter diagram (figure 2), there is a small negative correlation between the radioactive iodine excretion and the basal metabolic rate in thyrotoxic patients.

Specifically, the finding of a low urinary excretion of radioactive iodine aided in establishing the diagnosis of thyrotoxicosis in patients 3 and 9 (table 3). These were individuals in whom a diagnosis of hyperthyroidism could not be made with assurance clinically. The anatomic changes observed in the operatively removed thyroids and the symptomatic improvement with gain in weight by these patients following thyroidectomy leave little doubt as to the preëxistence of toxicity.

\* Three patients had thyrotoxicosis persisting after radioactive iodine therapy.



The finding of a high urinary excretion of radioactive iodine facilitated the exclusion of hyperthyroidism in cases No. 2, 6, 7, 8, 9, 10, 13, 14, 17, and 18 (table 2). These were patients in whom features of the history or clinical appearance were suggestive of thyrotoxicosis. A persistently elevated basal metabolic rate and an equivocal response to a therapeutic test with iodine further confused the diagnosis in a number of instances. One patient was a chronic alcoholic; two had anxiety neurosis; one had compensated arteriosclerotic heart disease; four, compensated hypertensive

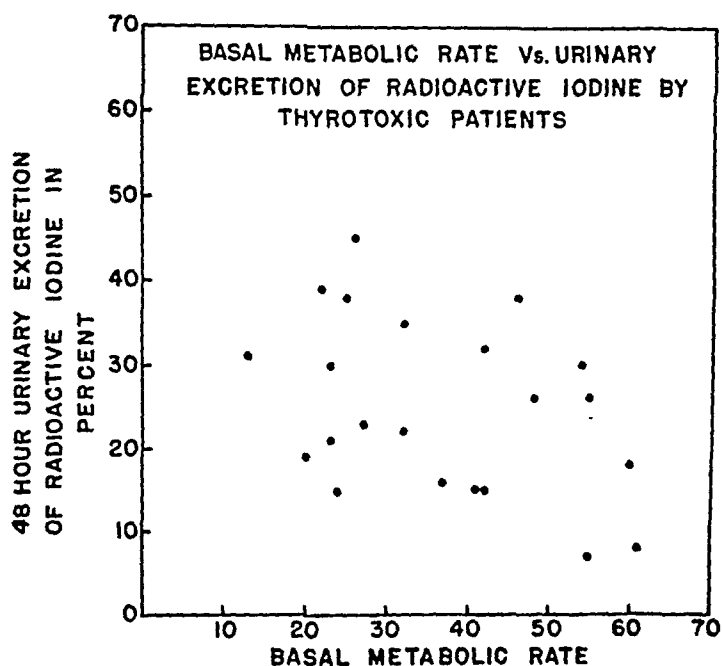


FIG. 2. Scatter diagram showing relation of basal metabolic rate to urinary excretion of radioactive iodine in thyrotoxic patients.

cardiovascular disease; one, Parkinsonism; and one, pheochromocytoma. One patient (No. 17, table 2) had a nodular goiter, an elevated basal metabolic rate and an elevated blood iodine due to a cholecystogram done some months previously.

Survey of the body with the Geiger counter yielded important information in two toxic patients in whom no thyroid tissue could be palpated in the neck. Case No. 15 (table 2) was that of a female patient who had undergone subtotal thyroidectomy for Graves' disease 10 years before admission. Two fruitless explorations of the neck had been done subsequently at an outside hospital for "recurrent thyrotoxicosis." At entry, the patient presented the classic appearance of Graves' disease except for the absence of goiter. *Struma ovarii* was suspected because of slight enlargement of the right ovary. Search with the Geiger counter disclosed no iodine-concentrating tissue anywhere in the body, and virtually the entire tracer dose of iodine was excreted within 48 hours. The diagnosis of thyrotoxicosis *factitia* was confirmed by the finding of tablets of desiccated thyroid in the patient's possession and by

the rapid fall in the basal metabolic rate and the serum protein-bound iodine upon withdrawal of this desiccated thyroid.

Case No. 4 (table 3) was that of a male patient with moderately severe thyrotoxicosis in whom the propriety of exploring the neck was debated because of the absence of palpable thyroid tissue. Heavy external gamma radiation from the cervical region was detected by the Geiger counter after the administration of radioactive iodine, and at operation a small quantity of hyperplastic thyroid tissue, weighing 19 gm., was found.

### DISCUSSION

The proportion of a test dose of iodine excreted in the urine within a given time is dependent upon: (1) the avidity of the thyroid gland for iodine, and (2) a variety of extrathyroidal factors, among which are the quantity and type of iodine compound administered, the rate of absorption of iodine, and the state of kidney function. When radioactive iodine is employed the existence of the radioactivity may influence the physiological processes under study.

An increased avidity for iodine is possessed by hyperplastic thyroid glands with a low iodine content from any cause.\* Confirmation of this fact has been obtained with radioactive tracer technics both in experimental animals<sup>11</sup> and in patients.<sup>9, 12</sup> The existence of clinical hyperthyroidism is therefore not a necessary corollary to the demonstration of increased iodine tolerance.

Among the extra-thyroidal factors affecting the urinary excretion of a test dose of iodine, it is clear that the quantity of iodine administered is of major importance. The percentage of iodine collected by the normal thyroid varies inversely with the size of the dose.<sup>3</sup> In previously untreated patients with Graves' disease, the initial collection of iodine has been reported to approximate 100 per cent for small doses (0.2 to 5.0 mg.) while the initial collection from larger doses is considerably smaller.<sup>14</sup> The dosage factor doubtless accounts, in part, for the magnitude of the difference in urinary iodine excretion between euthyroid and hyperthyroid individuals reported by the various investigators in table 1. Administration of the smallest possible dose of iodine compatible with accurate measurement would seem to promise optimal sensitivity.

Since all of the iodine tolerance procedures have employed iodide as the test substance, the type of iodine compound administered can be neglected.

The rate of absorption of iodide from the gastrointestinal tract of normal individuals is extremely rapid. The blood iodine concentration reaches its peak within 30 minutes when doses of 2 gm. or more of potassium iodide are ingested.<sup>15</sup> The peak is not attained until 90 minutes after the ingestion of 0.5 gm. of potassium iodide.<sup>16</sup> Radioactivity is detectable in the hand within three to six minutes after the ingestion of 250 mg. of sodium iodide labelled

\* Unless iodine uptake be blocked by an agent such as thiouracil.

with radioactive iodine and absorption is apparently complete within three hours.<sup>17</sup> Precise data regarding the absorption of the very much smaller doses of iodide administered in these iodine tolerance tests are not available.

The state of renal function may significantly affect the excretion of iodide. According to Salter,<sup>18</sup> the urinary excretion of an administered dose of iodine is retarded in patients with renal damage. Inasmuch as experimental passive congestion of the kidneys has been shown to retard the excretion of iodine,<sup>19</sup> the urinary excretion test is presumably invalid in the presence of cardiac decompensation.

The low correlation found between the urinary excretion of radioactive iodine and the basal metabolic rate in thyrotoxic patients merits particular comment. That only one component of the basal oxygen consumption is ascribable to thyroid activity has long been known. It seems clear that the iodine tolerance test is not measuring precisely the same function as the metabolic rate. Which measure of thyroid function possesses the greater intrinsic validity cannot be deduced from the facts currently available. The low correlation between the two variables proved clinically advantageous in a number of instances (cases No. 3, 9, 19, and 23, table 3). These were patients in whom the elevation of the basal metabolic rate was minimal but in whom the low urinary excretion of radioactive iodine provided decisive evidence for the presence of thyrotoxicosis.

### CONCLUSIONS

1. The mean urinary excretion of radioactive iodine by 22 thyrotoxic patients was 25 per cent, range 7 per cent to 45 per cent.

2. The mean urinary excretion of radioactive iodine by 30 non-thyrotoxic patients was 60 per cent, range 23 per cent to 98 per cent.

3. There is considerable overlapping in the radioactive iodine excretion between thyrotoxic and non-thyrotoxic individuals in the range 20 to 40 per cent.

4. The finding of a low urinary excretion of radioactive iodine aided in establishing the diagnosis of Graves' disease in clinically equivocal cases. The finding of a high urinary excretion of radioactive iodine was of assistance in excluding Graves' disease in borderline cases in whom a truly basal metabolic rate could not be obtained. Specifically, the exclusion of Graves' disease has been facilitated in patients exhibiting hypermetabolism due to alcoholism, anxiety, compensated hypertensive cardiovascular disease, Parkinsonism, pheochromocytoma and thyrotoxicosis factitia. In that group of patients exhibiting an intermediate (20 to 40 per cent) excretion of radioactive iodine, the diagnosis of Graves' disease must be established by other clinical and laboratory findings.

5. Search for external gamma radiation with the Geiger-Müller counter following the administration of a tracer dose of radioactive iodine enables the location of thyroid tissue to be established when doubt exists.

## BIBLIOGRAPHY

1. MARINE, D., and FEISS, H. O.: The absorption of potassium iodide by perfused thyroid glands and some of the factors modifying it, *Jr. Pharmacol. and Exper. Therap.*, 1915, vii, 557-576.
2. MARINE, D., and ROGOFF, J. M.: The absorption of potassium iodide by the thyroid gland in vivo, following its intravenous injection in constant amounts, *Jr. Pharmacol. and Exper. Therap.*, 1916, viii, 439-444.
3. PERKIN, H. J., BROWN, B. R., and LANG, J.: The blood iodine content of normal and thyrotoxic individuals. An iodine tolerance test, *Canad. Med. Assoc. Jr.*, 1934, xxxi, 365-368.
4. WATSON, E. M.: An iodine tolerance test for the investigation of thyroid function, *Endocrinology*, 1936, xx, 358-362.
5. WATSON, E. M.: The relation of the iodine tolerance to thyroid function, *Endocrinology*, 1938, xxii, 528-537.
6. PERKIN, H. J., and LAHEY, F. H.: The iodine tolerance test as an aid in the diagnosis of clinical hyperthyroidism, *New England Jr. Med.*, 1937, ccxvi, 501-513.
7. PERKIN, H. J., LAHEY, F. H., and CATTELL, R. B.: Blood iodine studies in relation to thyroid disease. Basic concept of the relation of iodine to the thyroid gland; an iodine tolerance test, *New England Jr. Med.*, 1936, ccxiv, 45-52.
8. HERTZ, S., and ROBERTS, A.: Radioactive iodine as an indicator in thyroid physiology. V. The use of radioactive iodine in the differential diagnosis of the two types of Graves' disease, *Jr. Clin. Invest.*, 1942, xxi, 31-32.
9. HAMILTON, J. G., and SOLEY, M. H.: Studies in iodine metabolism by the use of a new radioactive isotope of iodine, *Am. Jr. Physiol.*, 1939, cxxvii, 557-572.
10. ELMER, A. W.: Iodine metabolism and thyroid function, 1938, Oxford Univ. Press, London.
11. LARSON, R. A., KEATING, F. A., JR., PEACOCK, W., and RAWSON, R. W.: A comparison of the effect of thiouracil and of injected thyrotropic hormone on the collection of radioactive iodine and the anatomic changes induced in the thyroid of the chick, *Endocrinology*, 1945, xxxvi, 149-159.
12. RAWSON, R. W., HERTZ, S., and MEANS, J. H.: Thiocyanate goiter in man, *Ann. Int. Med.*, 1943, xix, 829-842.
13. HERTZ, S., ROBERTS, A., MEANS, J. H., and EVANS, R. D.: Radioactive iodine as an indicator in thyroid physiology. II. Iodine collection by normal and hyperplastic thyroids in rabbits, *Am. Jr. Physiol.*, 1940, cxxviii, 568-576.
14. HERTZ, S., ROBERTS, A., and SALTER, W. T.: Radioactive iodine as an indicator in thyroid physiology. IV. The metabolism of iodine in Graves' disease, *Jr. Clin. Invest.*, 1942, xxi, 25-32.
15. FELLEBERG, TH. VON: Untersuchungen über den Jodstoffwechsel, *Biochem. Ztschr.*, 1926, clxxiv, 341-354.
16. VEIL, W. H., and STURM, A.: Beiträge zur Kenntnis des Jodstoffwechsels, *Deutsch. Arch. f. klin. Med.*, 1925, cxlvii, 166-223.
17. HAMILTON, J. G.: The rates of absorption of the radioactive isotopes of sodium, potassium, chlorine, bromine and iodine in normal human subjects, *Am. Jr. Physiol.*, 1938, cxxiv, 667-678.
18. SALTER, W. T.: The endocrine function of iodine, 1940, Harvard University Press, Cambridge, Mass.
19. ROWNTREE, L. G., FITZ, R., and GERAGHTY, J. T.: The effects of experimental chronic passive congestion on renal function, *Arch. Int. Med.*, 1913, xi, 120-147.

# PATHOGENESIS OF HUMAN BRUCELLOSIS WITH RESPECT TO PREVENTION AND TREATMENT \*

By WESLEY W. SPINK, M.D., F.A.C.P., *Minneapolis, Minnesota*

MEDICAL historians have informed us that brucellosis is a disease of antiquity, excellent clinical descriptions having been ascribed to Hippocrates.<sup>1</sup> However, it is only within recent years that human brucellosis has engaged the interest of clinicians in this country. Thus, in the two states of Iowa and Minnesota, where brucellosis is a serious endemic problem, the first human cases were recognized as recently as 1927. Brucellosis is a disease of major concern at the present time because there are indications that the incidence is on the increase both in domestic animals and in human beings. It has been estimated that the annual cost of this disease to the cattle industry alone in the United States amounts to almost \$100,000,000.<sup>2</sup> Although the precise number of cases of human brucellosis is not known, it is most significant that more cases were recognized and reported for the country as a whole during 1947, than during any previous year.<sup>3</sup> It is well then to consider briefly the pathogenesis of human brucellosis with relations to the natural reservoir of the disease; the modes by which human beings contract the disease; the basic tissue reactions following entrance of the microorganisms into the body; means for preventing the disease; and recent advances in treatment.

## EPIDEMIOLOGY OF BRUCELLOSIS

It is of fundamental importance to recognize that brucellosis, except under extremely rare conditions, is not transmitted from human to human. *The disease has its reservoir in domestic animals; particularly in cattle, hogs and goats.* Three closely related species of *Brucella* are the cause of human disease. Figure 1 illustrates certain basic concepts of the epidemiology of brucellosis. *Brucella melitensis*, often considered the most invasive of the three species of *Brucella*, is found primarily in goats. Because the disease localizes in the udder, the disease is transmitted to man through contact of the skin with contaminated milk, or through the ingestion of milk or milk products. Occasionally, *Br. melitensis* infects cattle. A very serious and disturbing problem relating to this species is based upon the recent findings in Iowa and in Minnesota in that *Br. melitensis* is widely distributed in hogs,

\* Presented at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, April 22, 1948.

From the Division of Internal Medicine, University of Minnesota Hospitals and Medical School, Minneapolis.

The investigations cited in this paper have been supported by grants from the United States Public Health Service; Committee on Scientific Research, American Medical Association; Graduate School, University of Minnesota; and the Commercial Solvents Corporation.

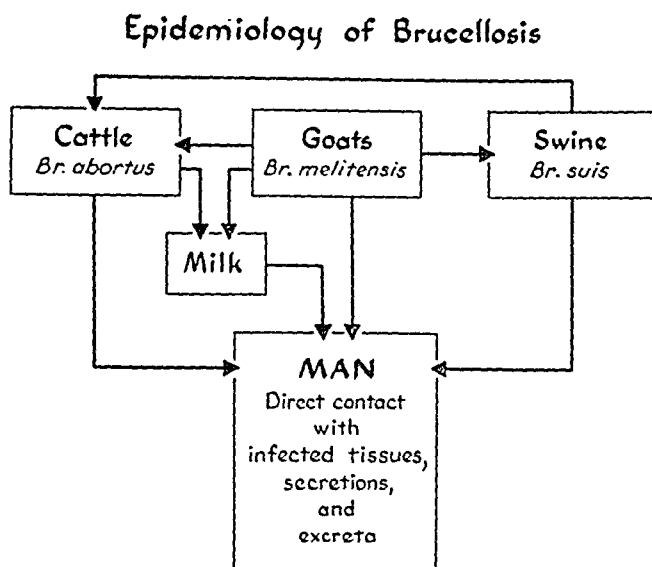


FIG. 1. The epidemiology of brucellosis.

and many human infections due to this species have occurred because of contact with infected porcine tissue.<sup>4, 5</sup> The hog is the natural reservoir for *Br. suis* and man contracts the disease through contact of the skin or mucous membranes with infected tissues or fluids from this animal. However, *Br. suis* also invades dairy cattle, and up until recently, the only serious known epidemics of human brucellosis due to cow's milk were traced to *Br. suis* infections in cattle.<sup>6, 7, 8</sup> *Brucella abortus*, frequently regarded as the least invasive of the species, localizes in the udder of cattle, and in the pregnant uterus of heifers. These features of bovine brucellosis account for human infections caused by drinking raw milk, and by contact with aborted material, uterine discharges and contaminated premises. Human infections due to *Br. abortus* are not always benign, as one is led to believe from a review of the literature. The disease, not infrequently, is severe, and fatal infections have been encountered at the University of Minnesota Hospitals. In most instances, *Br. abortus* causes sporadic infections, but it is highly significant that a major epidemic was recently described as being due to this species.<sup>9</sup> During the Christmas holidays of 1944, an epidemic of 28 human cases occurred in a small community in eastern Maryland. The outbreak was traced to a dairy which supplied raw milk to the community from an infected herd of cattle.

Briefly, then, man contracts brucellosis from infected domestic animals through two principal ways. One mode of infection is through the consumption of raw milk obtained from diseased animals, and also from milk products such as cheese produced from unpasteurized milk. A second avenue of infection is through contact of the skin with tissues, secretions, and excretions of animals with brucellosis. Occasionally, individuals become infected working in the laboratories with cultures of *Brucella*. There is

some evidence that brucellosis may be included among the air-borne infections, and disease may result from the inhalation of viable *Brucella*.

### TISSUE REACTIONS DUE TO BRUCELLA

A proper understanding of the natural history of any infectious disease is dependent upon the organs involved and the types of cellular reactions that the invading microbes induce. Such information is often of considerable aid in developing a therapeutic attack on the disease. Early investigations on the pathology of experimental or human brucellosis emphasized the constancy with which organs belonging to the reticulo-endothelial system were invaded by *Brucella*, including the spleen, liver, bone marrow and lymph nodes. A second feature of the histopathology of brucellosis that has been stressed is the intracellular parasitism of parenchymal cells by the microorganisms. The classical observations of Fabyan<sup>10</sup> revealed this intracellular invasion by *Brucella* in the experimentally infected guinea pig. Theobald Smith<sup>11</sup> called attention to "the localization and multiplication of bacteria within cells not having phagocytic function" and stated that this unchecked multiplication had a considerable advantage over the host. More recently, others have emphasized the intracellular proliferation of *Brucella* in the pathogenesis of the disease.<sup>12, 13, 14</sup> The application of these observations to human brucellosis has been bridged by Meyer,<sup>15</sup> who studied the tissues of a young man dying within the first three weeks of a fulminating infection. Massive infiltration of renal epithelial cells by *Br. suis* was demonstrated. Meyer stated "this selective intracellular parasitism in

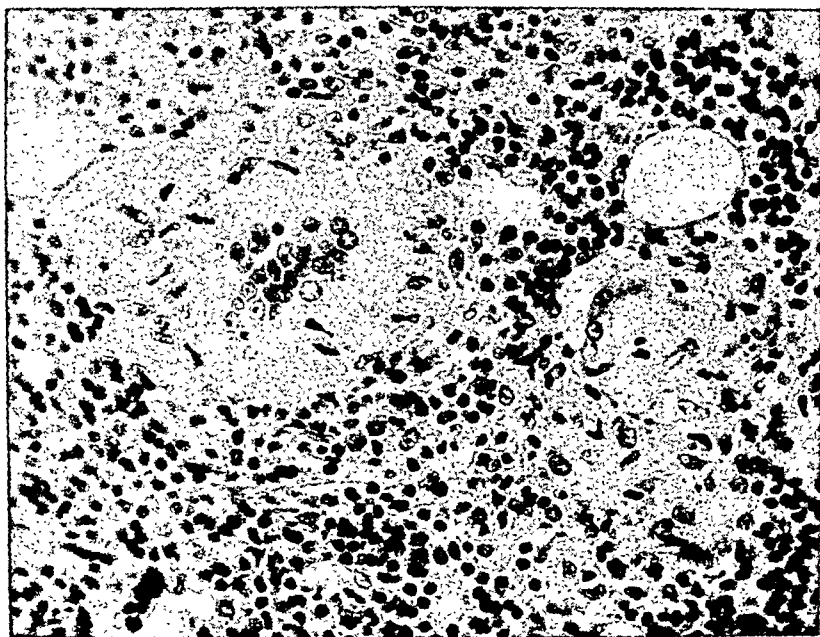


FIG. 2. Granulomatous nodule from sternal bone marrow aspiration showing epithelioid cells and giant cells.  $\times 400$ .

mesenchyme cells of various organs is doubtless of greatest significance in the pathogenesis of *Brucella* infections."

My associates and I have been interested in the pathogenesis of brucellosis with particular reference to the histopathology of the tissue reactions. Dr. A. I. Braude has demonstrated in the tissues of the guinea pig the intracellular invasion of hepatic cells by *Br. abortus* within one week after infection. This is confirmatory evidence that *Brucella* parasitize the so-called nonphagocytic tissue cells. Further studies have been carried out in our clinic to determine the type of reaction that occurs in human tissues as a result of brucellosis, especially in living subjects. Specimens of sternal bone marrow, lymph nodes and liver have been obtained from ambulatory patients by means of biopsy technics. The response of these tissues to invasion by

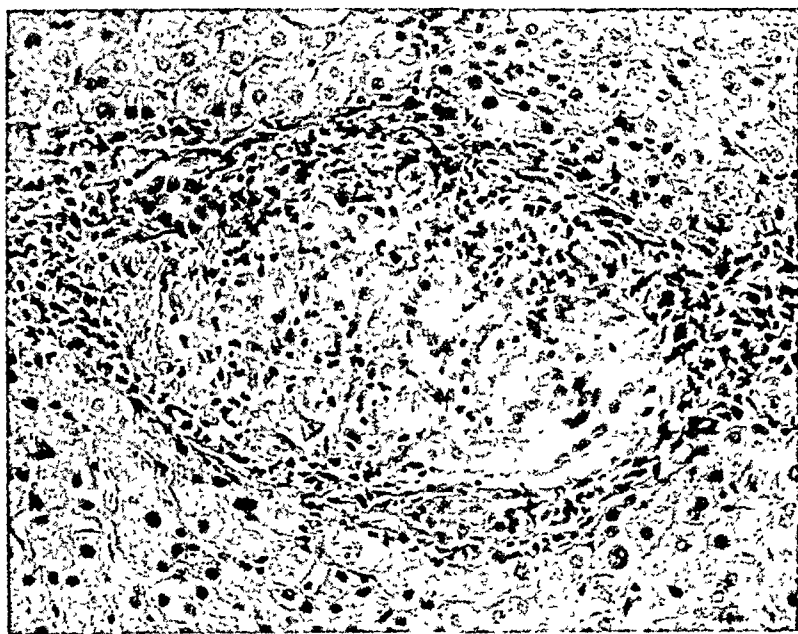


FIG. 3. Granulomatous lesion from human liver showing epithelioid cells and giant cells.  $\times 100$ .

*Brucella* has followed a constant type of cellular pattern. The outstanding feature is a proliferation of epithelioid cells, with or without the presence of giant cells of the Langhans and foreign body types, and the presence of lymphocytes, plasma cells, and occasionally, eosinophiles. Necrosis has not been a prominent feature. This type of tissue reaction is not specific for brucellosis and simulates that found in sarcoidosis and tuberculosis. The histopathology of the bone marrow in brucellosis has been reviewed in detail elsewhere with Dr. Dorothy Sundberg.<sup>10</sup> Figure 2 illustrates a nodule found in the marrow of a patient with brucellosis. Localization of *Brucella* in the sternal marrow may be of considerable aid in the diagnosis of brucellosis. Besides the tissue reactions which the organisms induce, cultures of marrow may yield *Brucella* when simultaneous blood cultures remain sterile.



*Brucella* have now been cultured from the sternal marrow in three patients in our clinic when repeated cultures of blood showed no growth of organisms.

Biopsies of the liver have been performed in a group of patients with brucellosis proved bacteriologically. These studies have been made with Dr. F. W. Hoffbauer and Dr. W. W. Walker, and it is significant that in every patient having active brucellosis, hepatic lesions have been seen in sectioned biopsy material. Two types of lesions have been encountered. The first is a periportal infiltration with lymphocytes and plasma cells, and occasional necrotic hepatic cells surrounded by mononuclear cells. The second type of lesion is similar to that which has been described for the bone marrow, and consists of epithelioid cells replacing the hepatic cells with occasional giant cells. Figure 3 represents a specimen of liver from a patient with chronic



FIG. 4. Sarcoid-like lesion in human spleen.  $\times 175$ .

brucellosis and shows a nodule comprised of epithelioid cells surrounded by a zone of lymphocytes. It has been stated that the most common visceral lesion occurring in brucellosis involves the liver.<sup>17</sup> On the basis of our own investigations thus far, we are inclined to believe these hepatic changes occur with such frequency in brucellosis that they cannot be considered as a complication, but rather, as a part of the natural history of the disease. Others have considered that brucellosis is at least a contributing factor in the genesis of cirrhosis of the liver.<sup>18, 19, 20, 21</sup> More and more evidence is accumulating in our clinic which would indicate that brucellosis not infrequently may be a contributing cause to serious, and even fatal, human cirrhosis of the liver.

In pursuing the study of the histopathology of brucellosis other tissues have been examined. Figure 4 illustrates a sarcoid-like lesion found in the

spleen of a patient who had a splenectomy carried out during the chronic phase of her illness. This procedure was without benefit to the patient. Figure 5 represents the same kind of a proliferation of epithelioid cells demonstrated in the excised lymph node of another patient.

Investigations conducted by Dr. A. I. Braude in our group in experimentally infected animals have also shown quite clearly that invasion of parenchymal tissue cells by *Brucella* is followed shortly by the appearance of nodular lesions comprised of epithelioid cells, giant cells and peripheral cellular aggregates of lymphocytes, plasma cells, and an occasional eosinophile cell. While hypersensitivity to *Brucella* antigen is a common feature of brucellosis, his observations reveal that this phenomenon is not essential

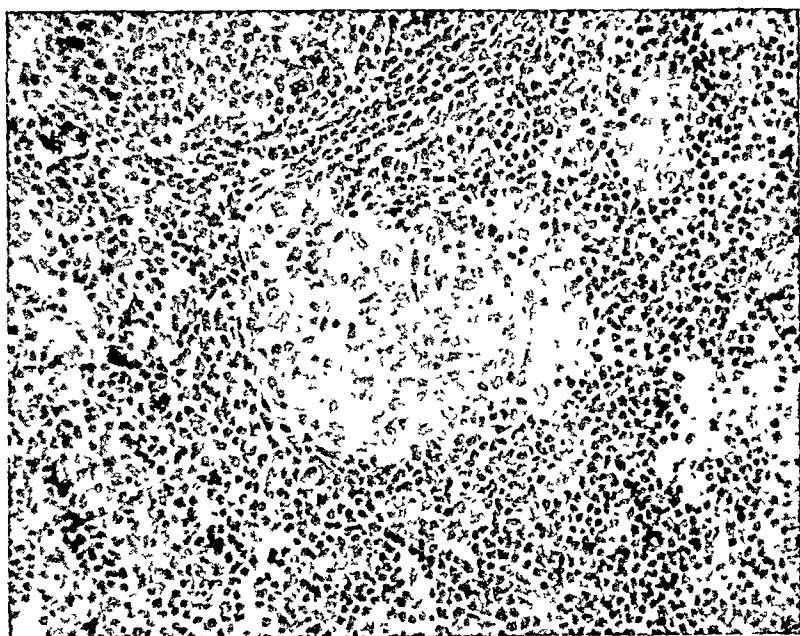


FIG. 5. Granulomatous lesion with epithelioid cells from human lymph node.  
× 225.

to the genesis of the granulomatous lesions of this disease. However, hypersensitivity of the tissues to some antigen or antigens of the bacterial cell appear to accelerate the formation of these lesions. It would appear that both in experimentally infected animals and in human brucellosis, the response on the part of the tissues with a proliferation of epithelioid cells without accompanying necrosis or caseation represents a desirable and efficient defense mechanism of the host against the invasion of the body by *Brucella*.

In addition to the foregoing granulomatous lesions in the various viscera, other more demonstrable complications of brucellosis have been observed. Prominent among these have been osseous changes involving the vertebrae, and the pelvic and long bones. It is becoming more and more apparent that osteolytic lesions of the spine may induce a symptom-complex of a herniated

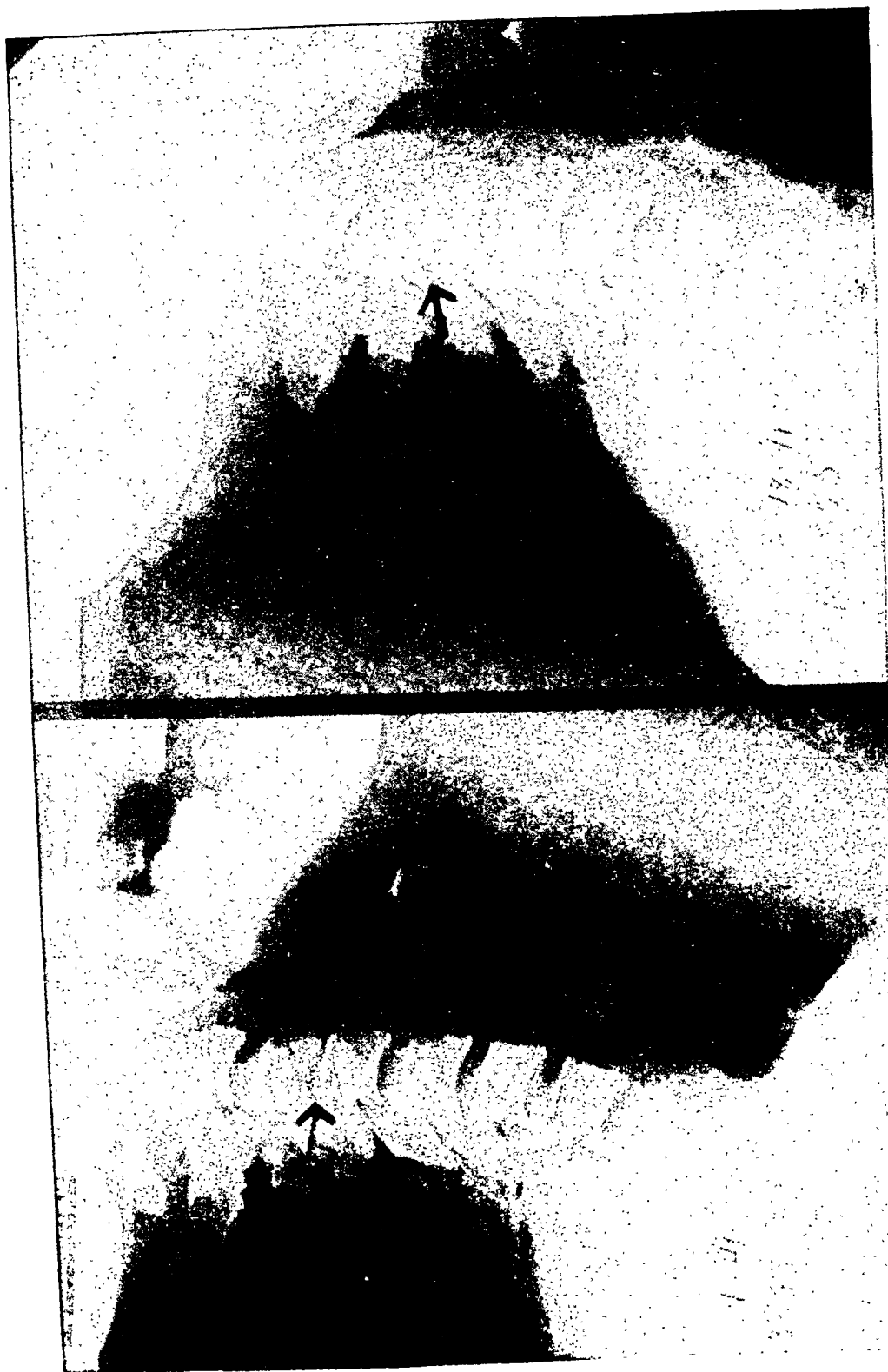


FIG. 6. Acute osteolytic Brucella lesion of cervical spine. X-ray film on right showing new bone formation taken one month after one on left.

intervertebral disc, spondylitis, or distribution of pain over the course of the sciatic nerve. In several instances, a destructive process of the intervertebral disc and adjacent vertebrae has been elicited roentgenologically. Figure 6 illustrates a destructive process in the cervical spine with repair taking place. It is of interest that those who have had extensive experience with infections due to *Br. melitensis* remark upon the infrequent occurrence of bone pathology due to this species.<sup>22, 23</sup> Similarly, osseous lesions do not appear to be too commonly associated with *Br. suis* infections, though by no means are they rare.<sup>24</sup> On the other hand, experience with cases of brucellosis in Minnesota over a period of ten years, which have been due mostly to *Br. abortus*, indicates that osseous pathology is a fairly frequent complication. This is in accord with observations in Uruguay where there is a predominance of brucellosis due to *Br. abortus*.<sup>25</sup> It should be emphasized that during the acute phase of brucellosis periarticular distress is frequently seen, but we have never encountered a single case of chronic arthritis which has resulted from brucellosis.

Another complication of brucellosis, which has been noted in our series of cases, is subacute bacterial endocarditis.<sup>26, 27</sup> Four cases due to *Br. abortus* have been studied and treated. Three of these patients had a fatal illness, but one of them has recovered and remained well for over a year following combined treatment with streptomycin and sulfadiazine.<sup>28</sup> Other less frequently observed complications have included encephalo-meningitis with recovery of *Br. abortus* from the cerebrospinal fluid in two cases; and a pericholecystic abscess due to *Br. suis*. Since symptoms in brucellosis are so commonly referable to the central nervous system, the cerebrospinal fluid should be studied and cultured more often, especially in the chronic cases. In our series of cases, two of our patients having chronic brucellosis with mental depression have committed suicide. Orchitis or epididymitis in the male has not been seen in our series; nor has abortion in the female occurred as a result of brucellosis.

#### IMMUNE REACTIONS DUE TO BRUCELLA

No attempt toward clarifying the pathogenesis of brucellosis would be complete without some discussion of the immune reactions that have been described. While much has been written and ably summarized, particularly by Huddleson,<sup>29</sup> on immunity in brucellosis, not a little confusion accompanies this aspect of the disease. One of the most outstanding features of human brucellosis is the consistency with which hypersensitivity develops following invasion of the tissues by *Brucella*. In fact, it is difficult to escape the conclusion that the symptomatology of brucellosis is due, in part at least, to a marked sensitivity of the tissues to a *Brucella* antigen or antigens. This sensitivity is most frequently demonstrated by intradermal tests with appropriate antigens, and very often following such a procedure the patient's symptomatology may be accentuated. The demonstration of dermal sen-

sitivity with or without systemic manifestations is oftentimes the basis for employing *Brucella* antigens for therapeutic purposes. Although it may not be illogical to subject patients with chronic brucellosis to increasing doses of *Brucella* antigens in attempts to "desensitize" their tissues, our own efforts in the therapy of brucellosis have been toward eradicating viable *Brucella* from the tissues, thus ridding the body of the source of antigenic material.

Another perplexing aspect of brucellosis is related to the question of natural and acquired immunity to the disease. It has been known for years that immature animals, such as young calves and young goats, are much more resistant to brucellosis than more mature animals, particularly pregnant cattle or goats. In lower animals, *Brucella* appear to have a predilection for embryonic tissues, mammary glands and for the pregnant uterus. Young children also appear to have a greater resistance to brucellosis than adults, although the former are repeatedly exposed to infective raw milk. Immune studies carried out in this clinic and elsewhere indicate that the tissues of rural children are invaded by *Brucella*, and mild infections are apparent in some cases, but the incidence of recognized brucellosis in any endemic area is much less under 12 years of age than in older age groups. Studies in progress in this clinic among rural families signify that some adults may also have a relative degree of natural resistance to the disease. On several occasions, it has been observed among closely knit groups exposed to the disease that only one or two individuals may develop acute brucellosis, although immunological studies indicate the remaining persons have been infected. Accurate information is not available as to whether an attack of brucellosis will protect an individual against subsequent exposure. Clinically, it is difficult to determine whether repeated attacks of brucellosis are due to a relapse of the initial disease or are due to a new infection. It would appear from observations made in this clinic on packing plant employees that repeated attacks of brucellosis do occur, and not infrequently, indicating that the immunity which does result from a single infection is only relative. It has now been clearly established that the injection of a viable strain of *Br. abortus* of low virulence into calves will offer a partial protection against subsequent exposure to Bang's disease. For obvious reasons, nothing is known about the protection that the injection of living *Brucella* might afford human beings. It has been fairly well decided that available preparations of killed *Brucella* do not provoke acquired immunity to the disease. It is apparent that more information is needed relative to the problems of natural and acquired brucellosis in human beings.

Although much has been written about the humoral immune reactions in brucellosis, their precise significance has often given rise to doubts because of unjustifiable interpretations placed upon them. The response to invasion of the tissues by *Brucella* that may be studied in the blood include opsonins, complement fixing antibodies and agglutinins. The most widely employed laboratory procedure for diagnostic purposes is the agglutination

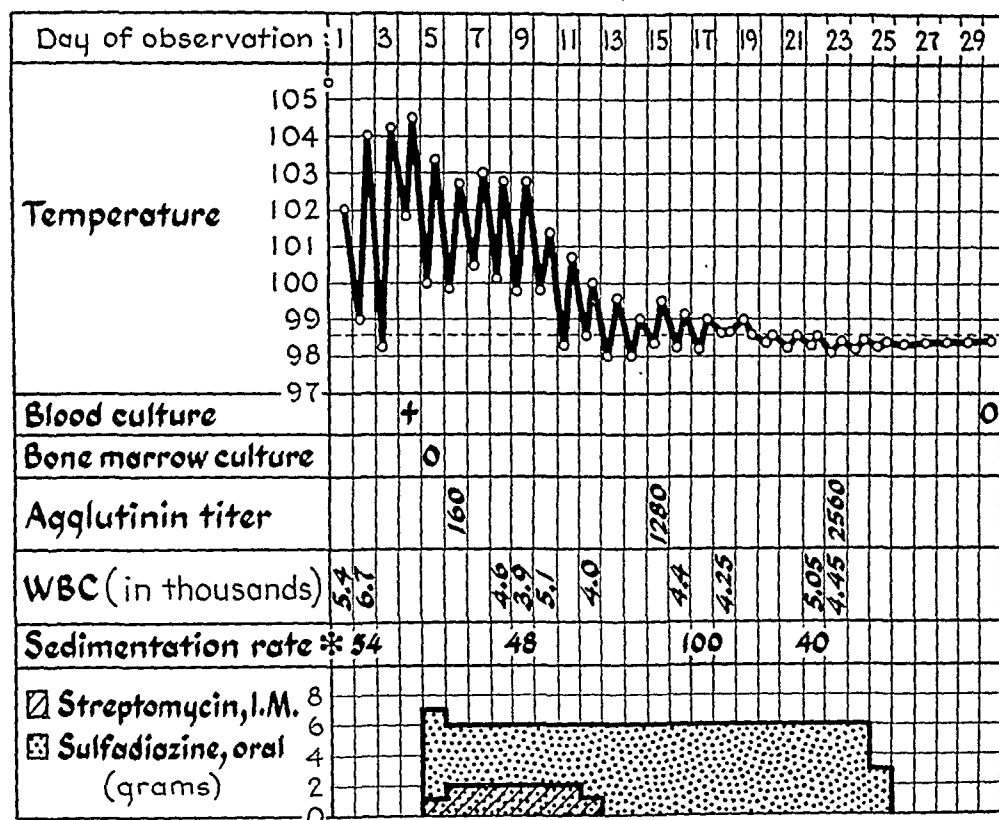
reaction. It is now recognized that the appearance of agglutinins in the serum in a titer of 1 to 100 and above has considerable diagnostic significance. On the other hand, these agglutinins may not necessarily be specific for *Brucella*, since cross reactions occur with *P. tularensis*, and Eisele and his group<sup>30</sup> have emphasized that immunization with cholera vaccine will result in a high titer of agglutinins for *Brucella*. Dr. W. H. Hall has demonstrated the presence of bactericidins against *Brucella* in the serum of normal individuals, that is, the undiluted and fresh serum will kill appreciable numbers of *Brucella*. In studying this phenomenon further, he has observed that fresh, undiluted serum from patients with the more chronic form of brucellosis uniformly exhibit a lack of killing power for *Brucella*. However, when the serum is diluted out, a prozone of killing action is found to be present. The significance of this prozone activity is still being investigated.

Briefly, then, the immunological aspects of brucellosis require further study and elucidation. Although certain serological reactions are of considerable aid in the diagnosis of active brucellosis, their limitations are too frequently overlooked. The nature and significance of hypersensitivity in the genesis of the symptom-complex of brucellosis also merits more attention.

#### TREATMENT OF BRUCELLOSIS

Effective therapy in human brucellosis calls for the administration of an agent or agents which will not only control the infection but which will eradicate *Brucella* from the body. In a previous communication, it was pointed out that the combined use of streptomycin and sulfadiazine gave more satisfactory therapeutic results than had been previously obtained at the University of Minnesota Hospitals over a period of 10 years.<sup>28</sup> The antibrucella effect of these two compounds was readily evaluated in the fertilized chicken egg.<sup>31, 32</sup> A continuation of these studies has revealed that the action of the combination of streptomycin and sulfadiazine is synergistic, and not merely additive.<sup>33</sup> To date, a number of other compounds in combination with streptomycin have been screened in infected embryos, and streptomycin and sulfadiazine still remain the most desirable ones for human purposes. It should be emphasized that in the infected fertilized hen's egg, the combination is effective against all three species of *Brucella*, namely, *Br. abortus*, *Br. suis*, and *Br. melitensis*.

To date, 17 patients with brucellosis have been treated with streptomycin and the sulfonamides, particularly with sulfadiazine. This group includes nine patients for whom the results of therapy were presented in a previous report.<sup>28</sup> These patients are again included in order to provide data on a longer follow-up period after the completion of therapy, which are so essential in the evaluation of treatment in brucellosis. For comparative purposes, the same numbers are given to the patients as those appearing in the first

V.N ♂ 57 yr. V.H.72781 *Duration of illness 3 wk.*

\* Millimeters per hour, Westergren

FIG. 7. Illustrating clinical course of patient with acute brucellosis treated with combination of streptomycin and sulfadiazine.

report on therapy. Pertinent data relating to the 17 patients are given in table 1. *Br. abortus* was isolated from 14 of the 17 patients. While organisms were not obtained in the cultures from the remaining three individuals, there was sufficient clinical and serological evidence to permit a diagnosis of active brucellosis. It has been approximately one year since the first patient was treated simultaneously with streptomycin and sulfadiazine at the University Hospitals. During this time, attempts have been made to answer several questions relative to this type of therapy. These have included the following: does the combination of streptomycin and sulfadiazine shorten the clinical course of acute brucellosis? Is the combination effective in chronic cases? Is such therapy of value in either acute or chronic cases when complications are in evidence? What is the optimum schedule of doses for each of the drugs? What toxic complications may one anticipate? How frequently will patients relapse following treatment? Is the development of streptomycin resistant strains of *Brucella* going to be a problem in therapy? It would appear that experience with 17 patients over a period of one year would provide at least a partial answer to the foregoing questions.

*Effect of Streptomycin and Sulfadiazine on the Clinical Course of Acute Brucellosis.* An arbitrary division of the patients into acute and chronic cases has been made by designating the acute form as an illness of less than three months in duration. Accordingly, nine of the patients had acute brucellosis, and *Br. abortus* was isolated from all the cases except case 41. It would be expected that the most favorable results would be obtained with the acute cases. Brucellosis is a disease with a variable clinical course. There may be a complete remission of the disease in an acutely ill patient

TABLE I

Summary as of April 1, 1948 of 17 Patients with Brucellosis Treated Simultaneously with Streptomycin and Sulfadiazine

Case No.	Age	Sex	Duration of Disease	Complications	Bacteriology	Treatment and Date of Completion	Comment
27	45	M	9 mos.	Subacute bacterial endocarditis	<i>Br. abortus</i> from blood 4 times	Streptomycin—52 gm. in 14 days; sulfadiazine—129 gm. in 22 days. Completed April 24, 1947.	Vertigo from streptomycin persists. Otherwise complete recovery and well for one year.
28	28	F	9 mos.	Radiculoneuritis left arm	<i>Br. abortus</i> from blood once; bone marrow once	Streptomycin—57 gm. in 15 days; sulfadiazine—120 gm. in 22 days. Completed April 18, 1947.	Complete recovery. No relapse one year after treatment.
29	28	M	2 mos.	Mesenteric adenitis with disabling right lower quadrant pain	<i>Br. abortus</i> from blood once	Streptomycin—22 gm. in 8 days; sulfadiazine—115 gm. in 20 days. Completed Aug. 4, 1947.	Complete recovery. No relapse 8 mos. after treatment.
30	32	M	9 mos.	Spondylitis and radiculitis	<i>Br. abortus</i> from blood once	Streptomycin—14.5 gm. in 8 days; sulfadiazine—142 gm. in 24 days. Completed Aug. 7, 1947.	Complete recovery. No relapse 7 mos. after treatment.
31	57	M	3 wk.	None	<i>Br. abortus</i> from blood once	Streptomycin—14 gm. in 8 days; sulfadiazine—124 gm. in 21 days. Completed April 28, 1947.	Complete recovery. No relapse in 11 mos.
32	25	M	2 mos.	None	<i>Br. abortus</i> from blood twice	Streptomycin—14 gm. in 7 days; sulfadiazine—76 gm. in 12 days. Completed Sept. 11, 1947.	Complete recovery—although spleen palpable at completion of treatment. No relapse in 6 mos.
33	31	F	2 mos.	Old mitral stenosis on rheumatic basis	<i>Br. abortus</i> from blood twice	Streptomycin—14 gm. in 7 days; sulfadiazine—102 gm. in 21 days. Completed Oct. 10, 1947.	Complete recovery. No relapse in 5 mos.
34	21	M	1 mo.	None	<i>Br. abortus</i> from blood 12 times	4 courses of therapy—1. Streptomycin—16.5 gm. in 9 days; sulfadiazine—66 gm. in 9 days. 2. Streptomycin—8 gm. in 4 days; sulfadiazine—20 gm. in 4 days. 3. Streptomycin—14 gm. in 7 days; sulfadiazine—62 gm. in 13 days. 4. Streptomycin—43.5 gm. in 15 days; sulfadiazine—87 gm. in 15 days. Total streptomycin 82 gm. in 35 days; sulfadiazine 235 gm. in 41 days. Completed Feb. 9, 1948.	Bacteriologic and clinical relapse after first 3 courses. No further relapse 2 mo. after fourth course. No change in in vitro resistance of <i>Br. abortus</i> isolated from blood to streptomycin after 3 courses of treatment.



TABLE I—Continued

Case No.	Age	Sex	Duration of Disease	Complications	Bacteriology	Treatment and Date of Completion	Comment
35	33	M	1 mo.	Femoral vein phlebothrombosis; pulmonary emboli with infarction; pulmonary effusion; pulmonary edema; lung abscesses; empyema; amebiasis	<i>Br. abortus</i> from blood twice	Streptomycin—77 gm. in 28 days; sulfadiazine—181 gm. in 25 days. Completed Sept. 24, 1947. Subsequently received streptomycin, sulfadiazine, penicillin, oxygen, and anticoagulants because of pulmonary suppuration secondary to pulmonary emboli.	18 blood cultures neg. for <i>Brucella</i> following treatment. Seriously ill with pulmonary suppuration not directly related to brucellosis. Recovering slowly.
36	25	M	1 week	None	<i>Br. abortus</i> from blood once	Streptomycin—19 gm. in 11 days; sulfadiazine—74 gm. in 13 days. Completed Oct. 27, 1947.	Complete recovery. No relapse in 5 mos.
37	60	M	3 mos.	None	<i>Br. abortus</i> from blood 5 times	Streptomycin—18 gm. in 9 days; sulfadiazine—132 gm. in 22 days. Completed Dec. 1, 1947.	Day after treatment completed <i>Br. abortus</i> from blood. 9 days after treatment, blood sterile. Feels well with no relapse in 4 mos.
38	31	M	4 mos.	None	<i>Br. abortus</i> from blood 4 times	Streptomycin—14.5 gm. in 7½ days; sulfadiazine—138 gm. in 24 days. Completed Dec. 31, 1947.	Complete recovery. No relapse in 3 mos.
39	32	M	9 mos.	Bone destruction rt. sacroiliac region	<i>Br. abortus</i> from bone marrow once	Streptomycin—28.5 gm. in 14 days; triple sulfonamide—130 gm. in 35 days. February 16, 1948.	Also bed rest for 3 weeks with extension of rt. leg. Marked improvement. Able to walk. No relapse in 7 weeks.
40	54	M	6 weeks	None	<i>Br. abortus</i> from bone marrow once	Streptomycin—30.8 gm. in 15 days; sulfadiazine—44.8 gm. in 15 days. Completed March 6, 1948.	Complete recovery. No relapse in 1 mo.
41	44	M	6 weeks	None	Blood culture sterile 8 times. Bone marrow sterile. Aggls. for <i>Br. abortus</i> 1:320	Streptomycin—14.5 gm. in 8 days; sulfadiazine—66 gm. in 14 days. Completed Aug. 25, 1947.	Sulfonamide discontinued because of drug fever and dermatitis. Complete recovery. No relapse in 7 mos.
42	40	M	13 mos.	None	Blood culture sterile 3 times. Bone marrow sterile. Aggls. for <i>Br. abortus</i> 1:320	Streptomycin—12 gm. in 7 days; triple sulfonamide—76 gm. in 19 days. Completed Jan. 16, 1948.	Complete recovery. No relapse in 2½ mos.
43	52	M	2 yr.	None	Blood culture sterile 2 times. Bone marrow sterile. Aggls. for <i>Br. abortus</i> 1:320	Streptomycin—14 gm. in 8 days; triple sulfonamide—68 gm. in 19 days. Completed Dec. 24, 1947.	Slight improvement. Weakness and sweats continued.

following a period of bed rest. For this reason, it is not too easy to interpret the results of therapy in case 31, whose clinical course is illustrated in figure 7. This individual had been ill for three weeks and after receiving streptomycin for eight days, and sulfadiazine for a total of 21 days, he recovered completely and has not had a relapse for 11 months. Because the patient became afebrile and abacteremic coincident with therapy, and has remained in good health for almost a year, it is believed that specific treatment in this instance did benefit the patient.

On the other hand, case 34 was a young individual who had been acutely ill for only one month. Although he had had adequate rest in bed, several courses of streptomycin and sulfadiazine were required before his illness appeared to be terminated. His course is presented in figure 8. In some respects, his illness simulated that observed in malaria. It is to be noted that following rest in bed his temperature declined and he felt so well that he prevailed upon the staff to permit him to attend a night football game. A few hours out in the brisk, open air was sufficient to precipitate a relapse of his brucellosis. In an attempt to evaluate a short course of streptomycin and sulfadiazine he was given both these drugs at the same time for only nine days. Shortly after completing treatment he suffered from another relapse. He was started on a second course but because of a death in his family, and improvement in his condition, treatment was continued for only four days, and he was allowed to attend the funeral. He had another relapse. Following an abbreviated third course of treatment, he had another relapse. But after a more intensive therapeutic schedule, he appears to have recovered. Other remarkable features of this case are that he did not develop any toxic reactions to either streptomycin or sulfadiazine, and the various cultures of *Br. abortus* isolated from his blood subsequent to the initiation of treatment did not reveal any diminution in in vitro sensitivity to streptomycin.

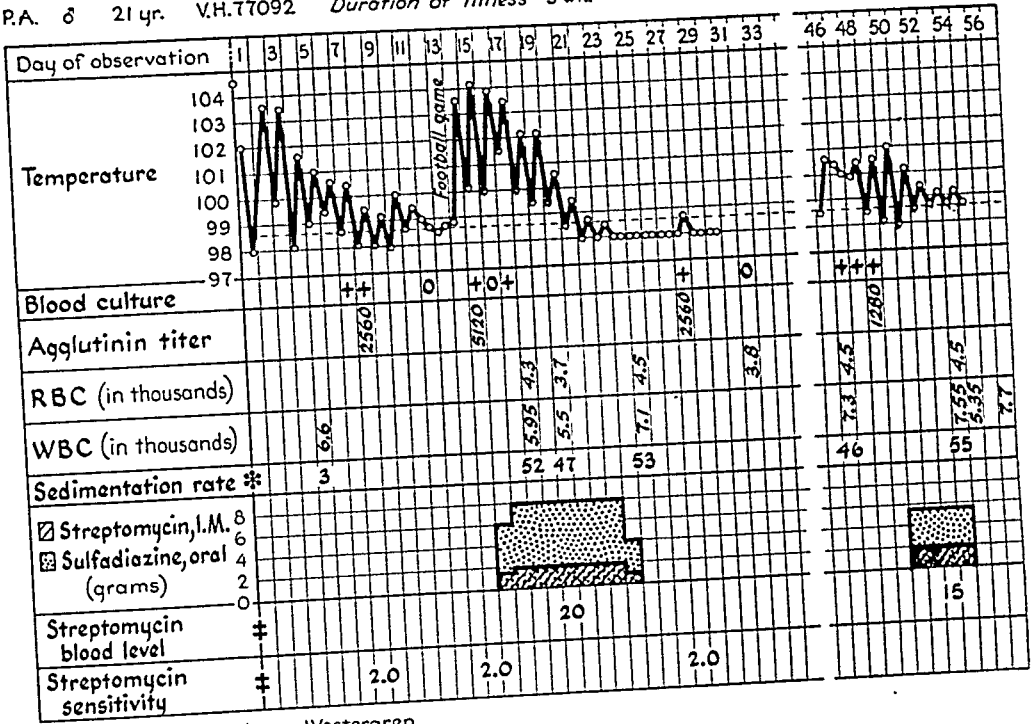
On the basis of observations in this group of nine cases with acute brucellosis, it takes from a week to 10 days of combined treatment before the patients experience definite improvement, and about that length of time before the temperature begins to assume normal values.

*Effect of Streptomycin and Sulfadiazine on the Clinical Course of Chronic Brucellosis.* Eight patients had an illness of three months or more, thus classifying them as chronic cases. *Br. abortus* was isolated from six of the eight patients. Contrary to expectations, the effect of therapy on the clinical course of this group of patients was similar to that obtained in the acutely ill patients, though slightly larger amounts of streptomycin were administered to the chronically ill patients.

Before any definite conclusions are formulated it is very apparent that further patients having chronic brucellosis of the type exhibited by cases 42 and 43 will have to be treated. These individuals represent the chronic state of brucellosis without definite localizing findings, and with negative cultural studies. In many instances of chronic brucellosis, the febrile response is absent or low-grade. We have been reluctant up to the present time to evaluate specific therapy in this type of case because in so many instances the precise diagnosis is always in doubt. Furthermore, it is in this type of case where abuses of therapeutic procedures have occurred in the past. We anticipate that streptomycin and sulfadiazine will be employed uncritically and without benefit in doubtful cases of chronic brucellosis.

*Effect of Streptomycin and Sulfadiazine on the Complications of Brucellosis.* Perhaps the most rigid test for any specific therapeutic procedure in

P.A. ♂ 21 yr. V.H.77092 Duration of illness 3 wk.



\* Millimeters per hour, Westergren  
+ Micrograms per cubic centimeter

P.A., cont.

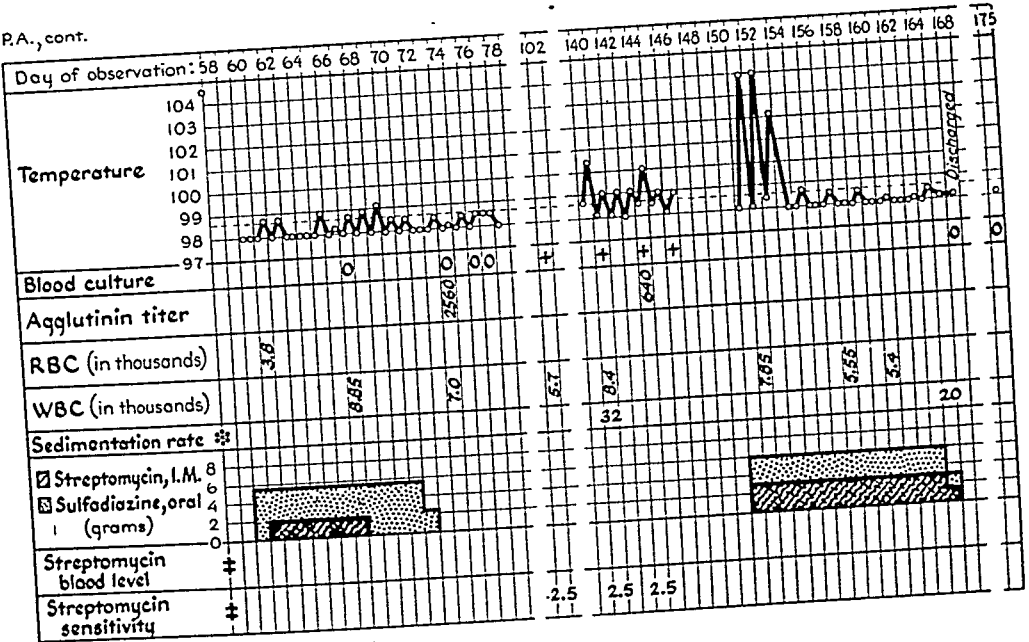


FIG. 8. Clinical course of patient with relapsing acute brucellosis. Apparent recovery after repeated treatment with combination of streptomycin and sulfadiazine. Note failure of *Br. abortus* to develop resistance to streptomycin.

brucellosis relates to the effect on some of the more severe complications. The second patient to receive the combined therapy in our clinic was an individual with subacute bacterial endocarditis due to *Br. abortus*. Experience with this complication in three previous patients had emphasized the futility of all prevailing therapy. Streptomycin and sulfadiazine in case 27 have resulted in a remission that has now lasted for one year. This individual has apparently recovered from a heretofore fatal complication of brucellosis.

Case 28 had been quite ill for nine months spending most of the time in bed. She had only partial use of her left arm because of a radiculoneuritis. This abated shortly after instituting combined treatment and she has remained well for one year.

Case 29 had an unusual type of complication in the form of recurrent and disabling pain in the right lower quadrant. Each attack was associated with fever, weakness, sweats and enlarged peripheral lymph nodes. While the diagnosis of intermittent appendicitis was entertained, it was concluded that there was simultaneous enlargement of the mesenteric lymph nodes along with the peripheral nodes to account for the pain. Following treatment, this patient has been free of pain or symptoms of the disease for eight months.

Infiltration of bone by *Brucella* may provoke a chronic illness which may be completely disabling as illustrated by cases 30 and 39. Case 30 had spondylitis of the lumbosacral area and an accompanying radiculitis. The pain was so severe that the daily administering of opiates was required. Before treatment was completed, this patient's pain had subsided to such a degree that he was able to rest without the aid of morphine. He recovered completely and has had no relapse in five months. Case 39 had a completely disabling and very painful destructive process of the right sacroiliac joint. Following treatment he was relieved of pain on walking, and within one month was able to work.

*Optimum Doses of Streptomycin and Sulfadiazine.* The treatment of 17 patients with the two drugs does not permit an unqualified statement as to optimum dose schedules. In the initial report, it was recommended that 0.5 gm. of streptomycin should be given intramuscularly every six hours for one week. At the same time that streptomycin is started, sulfadiazine is administered orally in an initial dose of 3 to 4 gm., and then 1 gm. every four hours for at least three weeks. Additional experience would indicate that the same six-hour dose of streptomycin should be given for two weeks, and sulfadiazine should be administered as stated for a total of three weeks. Whether such a schedule will prove adequate for all cases remains to be evaluated. It is recommended that the total daily dose of streptomycin should not exceed 2 gm. Larger doses may very well induce disagreeable and even disabling toxic reactions. It has been observed in this clinic by Miss Dorothy Anderson that the growth of freshly isolated strains of *Br. abortus* is consistently inhibited by 2 mcgm. of streptomycin or less per milliliter. One hour after injections of 0.5 gm. of streptomycin, serum

levels of 15 to 20 mcgm. are readily obtained. The foregoing doses of sulfadiazine yield levels of 7 to 10 mg. per cubic milliliter.

Thus far, the only toxic complication that has been ascribed to streptomycin occurred in case 27, who had subacute bacterial endocarditis, and who received up to 4 gm. of streptomycin a day for a total of 52 gm. in 14 days. This patient has involvement of the vestibular apparatus so that his equilibrium is disturbed making it difficult for him to carry out some of his duties as a farmer. This disturbance has persisted for a year, with little or no improvement since the onset. It was necessary to discontinue therapy with sulfadiazine in case 41 because of the appearance of fever and a dermatitis. Otherwise, no toxic reactions were related to sulfonamide therapy.

Because both streptomycin and sulfadiazine are drugs which may cause serious toxic complications, it is desirable that patients undergoing therapy should be treated in a hospital under close supervision. These precautions mean that the treatment of brucellosis is not inexpensive. Therefore, it is essential that the physician in attendance should be reasonably sure of his diagnosis.

*Relapses Following Treatment with Streptomycin and Sulfadiazine.* Since brucellosis is an illness which may subside spontaneously, only to manifest a relapse repeatedly, an evaluation of any specific therapy must take into consideration the incidence of relapses. Case 34 is an example of an acute case of brucellosis which was inadequately treated, and bacteriological and clinical relapses occurred. This case emphasizes the necessity of utilizing combined treatment for at least 14 days. Case 37 represented an instance of chronic brucellosis in which marked improvement occurred coincident with treatment, but immediately following the completion of therapy, a positive blood culture for *Br. abortus* was obtained. However, the patient has continued in a good state of health, and a subsequent culture of blood remained sterile. Case 43, representing a chronic case of brucellosis, manifested little or no improvement. It is possible that he might have benefited with a more prolonged course of treatment, especially with streptomycin. In this series of cases, then, the low relapse rate has been quite encouraging.

*Development of Resistance of Brucella to Streptomycin.* Microorganisms in general have a remarkable tendency to develop increased resistance to streptomycin as a result of therapy.<sup>34</sup> In a case not included in this series, Hall and Spink<sup>35</sup> observed a patient from whose blood a streptomycin-sensitive strain of *Br. abortus* was obtained. Following a month's therapy with streptomycin, several cultures of blood revealed the presence of a strain of *Br. abortus* which was highly resistant to the in vitro action of streptomycin. It was apparent, then, that resistance to streptomycin could develop as a result of treatment. However, subsequent studies included in this report, have not revealed another instance of such acquired resistance. In two cases, 34 and 37, *Brucella* were studied in vitro after treatment with streptomycin and there was no diminution of sensitivity of the organisms

to the drug. It is possible that resistance to either streptomycin or sulfadiazine is less likely to develop when both are administered simultaneously.

### PREVENTION OF BRUCELLOSIS

Human brucellosis will always constitute a problem in clinical medicine as long as the reservoir for the disease persists in domestic animals. As much support as possible should be given to the efforts to eradicate the animal reservoir of the disease. In cattle, no single plan of elimination will be effective under all conditions. The area testing of herds of cattle, with slaughtering of positive reactors, is essential under certain circumstances. Immunization with strain 19 of *Br. abortus* should be encouraged in young stock. The extermination of brucellosis in swine is beset with more difficult problems. Wiping out brucellosis in goats should not be too great a problem in this country, mainly because the goat population is concentrated west of the Mississippi in the southwestern states. It is quite clear that the eradication of the animal reservoir of brucellosis will require the combined support of farmers, livestock producers, veterinarians, packing plant authorities and public health officials.

Since it is not unlikely that the animal reservoir of brucellosis will be a threat for some years to come, efforts should be made to prevent the transmission of brucellosis to human beings. It is well established that a significant segment of the general population contracts the disease through drinking unpasteurized cows' milk, ingesting raw cream or cream products, and eating cheese prepared from unpasteurized goats' milk. Therefore, the medical profession should encourage the pasteurization of all animal milk used for human consumption. Strict legislation is essential to accomplish this, and the opposition in some quarters will not be mild. It is appropriate to call attention at this meeting of the American College of Physicians in San Francisco that in 1917 Fleischner and Meyer<sup>36</sup> pointed out that practically all the certified milk in the San Francisco Bay regions contained *Br. abortus*. Thirty years later, Dr. Karl Meyer has stated that all milk used for human consumption should be pasteurized because of the continued menace of brucellosis.<sup>37</sup>

Another segment or segments of the population are being exposed to brucellosis because of their contact with diseased animals. This makes brucellosis an occupational disease for farmers, livestock workers, veterinarians and those working in slaughter houses. It should be admitted that at the present time under these circumstances there are no practical means for protecting susceptible individuals from contracting the disease from infected animals. The solution of this problem ultimately resides in the elimination of brucellosis from the animals. No dependable methods of immunization against brucellosis for man are available.

## SUMMARY AND CONCLUSIONS

1. Human brucellosis is a major problem in public health in some sections of this country. There are indications that the incidence of the disease is on the increase.

2. The reservoir of the disease resides in domestic animals, especially cattle, swine and goats. The disease is transmitted either directly or indirectly to human beings from infected animals, and very rarely, if at all, from human to human.

3. Intracellular parasitism results from the invasion of tissues by *Brucella* resulting in the characteristic, but not specific, tissue reaction of proliferation of epithelioid cells and giant cells. In addition, complications include destructive osseous lesions, subacute bacterial endocarditis, encephalitis, and grossly suppurative lesions.

4. Hypersensitivity of the tissues to an antigen or antigens of *Brucella* is a constant feature of brucellosis, and the symptom-complex of the disease may depend, in part at least, upon this state of hypersensitivity.

5. The most satisfactory treatment to date for both acute and chronic cases of brucellosis is a combination of streptomycin and sulfadiazine. Thus far, 17 patients have been treated with a maximum follow-up period of one year. The following conclusions appear justified at the present time: *a.* The clinical course of both acute and chronic brucellosis is shortened by this combined therapy. *b.* The combination is effective against such complications of brucellosis as subacute bacterial endocarditis and spondylitis. *c.* Optimum doses remain to be worked out, but at present it is recommended that 0.5 gm. streptomycin be given intramuscularly every six hours for two weeks. At the same time that therapy with streptomycin is started, 3 to 4 gm. of sulfadiazine should be administered orally, and then 1 gm. every four hours for a total of two weeks. Toxic complications from streptomycin have not been encountered in patients receiving a maximum of 2 gm. per day.\* Thus far, streptomycin-resistant strains of *Brucella* have not been recovered from patients as a result of combined therapy.

6. The ultimate elimination of human brucellosis depends upon eradicating the disease from domestic animals. All efforts along this direction should be vigorously supported by the medical profession. This will take time to accomplish. In the meantime, other preventive means should be demanded such as the compulsory pasteurization of all milk destined for human consumption, and the pasteurization of all milk utilized for the production of butter and cheese.

## BIBLIOGRAPHY

1. EYRE, J. W. H.: The Milroy Lectures on Melitensis Septicaemia, *Lancet*, 1908, clxxiv, 1677.
2. MINGLE, C. K.: Personal communication.
3. Incidence of disease, *Pub. Health Rep.*, 1948, lxiii, 59.

\* Since this manuscript was submitted for publication an instance of vestibular dysfunction has been encountered in a patient receiving 2 gm. daily for 14 days.

4. JORDAN, C. F., and BORTS, I. H.: Occurrence of *Brucella melitensis* in Iowa, Jr. Am. Med. Assoc., 1946, cxxx, 72.
5. KABLER, P., BAUER, H., and NELSON, C. B.: Human *Brucella melitensis* infections in Minnesota with hogs as the probable source, Jr. Lab. and Clin. Med., 1947, xxxii, 854.
6. BEATTIE, C. P., and RICE, R. M.: Undulant fever due to *Brucella* of the porcine type—*Brucella suis*. Report of a milk-borne epidemic, Jr. Am. Med. Assoc., 1934, cii, 1670.
7. HORNING, B. G.: Outbreak of undulant fever due to *Brucella suis*, Jr. Am. Med. Assoc., 1935, cv, 1978.
8. BORTS, I. H., HARRIS, D. M., JOYNT, M. F., JENNINGS, J. R., and JORDAN, C. F.: A milk-borne epidemic of brucellosis caused by the porcine type of *Brucella* (*Brucella suis*) in a raw milk supply, Jr. Am. Med. Assoc., 1943, cxxi, 319.
9. STEELE, J. H., and HASTINGS, J. W., SR.: Report of brucellosis outbreak at Federalsburg, Maryland, U. S. Public Health Rep., 1948, lxiii, 144.
10. FABYAN, M.: A contribution to the pathogenesis of *B. abortus*, Bang-II, Jr. Med. Research, 1912, xxvi, 441.
11. SMITH, T.: A characteristic localization of *B. abortus* in the bovine fetal membranes, Jr. Exper. Med. 1919, xxix, 451.
12. GOODPASTURE, E. W., and ANDERSON, K.: The problem of infection as presented by bacterial invasion of the chorio-allantoic membrane of chick embryos, Am. Jr. Path., 1937, xiii, 1949.
13. BUDDINGH, G. J., and WOMACK, F. C., JR.: Observations on the infection of chick embryos with *Bacterium tularense*, *Brucella* and *Pasteurella pestis*, Jr. Exper. Med., 1941, lxxiv, 213.
14. CASTANEDA, M. R.: Studies on the pathogenesis of brucellosis, Proc. Soc. Exper. Biol. and Med., 1947, lxiv, 298.
15. MEYER, K. F.: Observations on the pathogenesis of undulant fever, essays in biology, 1943, University of California Press, Berkeley and Los Angeles, p. 437.
16. SUNDBERG, R. D., and SPINK, W. W.: The histopathology of lesions in the bone marrow of patients having active brucellosis, Blood, Jr. of Hematology, Supp. No. I, 1947, p. 7.
17. MICHEL-BECHET, R.: Localizations viscerales et aspects chirurgicaux des brucelloses, 1939, Masson et Cie, Paris, p. 39.
18. WOHWILL, F.: Zur pathologischen Anatomie der Bangeskrankung des Menschen, Virchow's Arch. f. path. Anat. u. Physiol., 1932, cclxxxii, 141.
19. DIEHL, F., and ROTH, F.: Hepatolienale Syndrome bei Bangscher Krankheit, Deutsch. Arch. f. klin. Med., 1935, clxxviii, 271.
20. HANTSCHMANN, L.: Die Bang'sche Krankheit des Menschen, Zentralbl. f. inn. Med., 1936, lvii, 393.
21. AYOLA, A. A.: Contribucion al estudio de las Hepatocirrhosis Melitococicas, Med. Clin., 1945, v, 201.
22. HUGHES, M. L.: Mediterranean, Malta or undulant fever, 1897, Macmillan Co., Limited, London, p. 139.
23. CASTANEDA, M. R.: Personal communication.
24. HARDY, A. V., JORDAN, C. F., BORTS, I. H., and HARDY, G. C.: Undulant fever with especial reference to a study of *Brucella* infection in Iowa, Nat. Inst. Health Bull. No. 158, 1930, p. 57.
25. PURRIEL, P., RUSSO, R., and ESPASONDIN, J.: Brucelosis. Estudio de Esta Enfermedad en el Uruguay, 1944, Editorial Independencia, p. 237.
26. SPINK, W. W., and NELSON, A. A.: *Brucella* endocarditis, Ann. Int. Med., 1939, xiii, 721.
27. SPINK, W. W., TITRUD, L. A., and KABLER, P.: A case of *Brucella* endocarditis with clinical, bacteriologic, and pathologic findings, Am. Jr. Med. Sci., 1942, cciii, 797.
28. SPINK, W. W., HALL, W. H., SHAFFER, J. M., and BRAUDE, A. I.: Human brucellosis. Its specific treatment with a combination of streptomycin and sulfadiazine, Jr. Am. Med. Assoc., 1948, cxxxvi, 382.



29. HUDDLESON, I. F.: Immunity in brucellosis, *Bact. Rev.*, 1942, vi, 111.
30. EISELE, C. W., McCULLOUGH, N. B., BEAL, G. A., and ROTTSCHAEFFER, W.: Brucella agglutination tests and vaccination against cholera, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 983.
31. HALL, W. H., and SPINK, W. W.: Therapy of experimental Brucella infection in the developing chick embryo: I. Infection and therapy via the allantoic sac, *Jr. Immunol.* In press.
32. SHAFFER, J. M., and SPINK, W. W.: Therapy of experimental Brucella infection in the developing chick embryo. II. Infection and therapy via the yolk sac, *Jr. Immunol.* In press.
33. SHAFFER, J. M., and SPINK, W. W.: Therapy of experimental Brucella infection in the developing chick embryo: III. The synergistic action of streptomycin and sulfadiazine, *Jr. Immunol.* In press.
34. PAIN, T. F., MURRAY, R., and FINLAND, M.: Streptomycin. II. Clinical uses, *New Eng. Jr. Med.*, 1947, ccxxxvi, 748.
35. HALL, W. H., and SPINK, W. W.: In vitro sensitivity of Brucella to streptomycin: Development of resistance during streptomycin treatment, *Proc. Soc. Exper. Biol. and Med.*, 1947, lxiv, 403.
36. FLEISCHNER, E. C., and MEYER, K. F.: Observations on the presence of the *Bacillus abortus bovinus* in certified milk, *Am. Jr. Dis. Child.*, 1917, xiv, 157.
37. MEYER, K.: In Diseases transmitted from animals to man by T. G. HULL, 1947, Charles C. Thomas, Springfield, p. 115.

# HOARSENESS IN HEART DISEASE \*

By J. LAWN THOMPSON, JR., M.D., F.A.C.P., and ALBERT D. KISTIN, M.D., *Washington, D. C.*

LEFT recurrent laryngeal nerve palsy in association with heart disease is apparently very uncommon. Review of the literature reveals sporadic reports. We have been able to find only 30 cases in which necropsy findings are recorded. Mitral stenosis, coronary arteriosclerotic heart disease with congestive failure, and congenital heart disease with pulmonary artery dilatation are among the etiological factors reported. From a review of the literature and study of the cases herein reported it is apparent that dilatation of the pulmonary artery is the prime cause of the nerve injury. Other common cardiovascular abnormalities causing left recurrent laryngeal nerve palsy (manifested by hoarseness) are aneurysm of the arch of the aorta and aneurysm of the innominate or subclavian arteries. In each of our cases the only complaint at time of hospitalization was that of hoarseness. This is significant, because it brings into focus heart disease as an important consideration in the differential diagnosis of that complaint. Two cases are herein reported, one with autopsy findings and the other with angiocardio-graphic studies in which the evidence favors the conception that pulmonary artery dilatation is the major mechanism in the compression and subsequent degeneration of the left recurrent laryngeal nerve.

## CASE REPORTS

*Case 1.* M. B. C., age 30, was admitted to the hospital complaining of hoarseness of three weeks' duration. The past history revealed no significant illness except that of asthma for which he had been discharged from the Army two years previously. The physical examination revealed the following significant points: The heart was enlarged downward and to the left, the point of maximal impulse being 15 cm. from the mid-sternal line in the fifth intercostal space; there was a soft diastolic murmur heard in the mitral area with an associated harsh systolic murmur, the latter murmur being transmitted to the base of the left lung posteriorly; there was an aortic diastolic murmur heard best to the left of the sternum in the third intercostal space. The blood pressure in each arm was 100 mm. Hg systolic and 50 diastolic. The lung fields were clear throughout. Laryngoscopic examination revealed flaccid paralysis of the left vocal cord. Roentgen-ray examination revealed an enlarged triangular-shaped heart shadow in the postero-anterior view, while in the right oblique view there was slight posterior displacement of the esophagus and a very prominent pulmonary segment (figure 1). An electrocardiogram done at this time was interpreted as being normal.

\* Received for publication August 8, 1947.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, who assumes no responsibility for opinions expressed or conclusions drawn by the authors.

From the Medical Service and the Cardiovascular Research Unit, Veterans Administration Hospital, Washington, D. C.

Six months later the patient was readmitted complaining of a cough productive of blood-tinged sputum and of marked shortness of breath. The physical examination revealed essentially the same cardiac findings but there were noted moist râles at the bases of the lungs, bilaterally. There was no evident peripheral edema. The course in the hospital revealed daily temperature elevations to  $101^{\circ}$ , and the spleen was soon



FIG. 1. Case 1. Roentgenogram of the chest, right anterior oblique view with barium-filled esophagus. There is slight posterior displacement of the esophagus indicating slight enlargement of the left atrium (AL). The pulmonary segment (PS) is very prominent.

noted to become palpable. Blood cultures were consistently negative, the course was rapidly downward, and death ensued.

Pertinent postmortem findings: The body was well nourished and well developed. There was moderate cyanosis.

Heart: The heart was markedly enlarged. In situ, the upper part of the left border was convex and consisted of pulmonary artery. Most of the anterior surface



FIG. 2. *Case 1.* Photograph of dissection. Anterior view. The left lung has been retracted and the heart has been rotated slightly clockwise as seen from above. For demonstration the flattened, discolored portion of the left recurrent laryngeal nerve has been pulled up from its original location between the arch of the aorta and the left pulmonary artery. A—arch of aorta. I—innominate artery. LCC—left common carotid artery. LS—left subclavian artery. V—vagus nerve. LA—ligamentum arteriosum. PA—pulmonary artery showing dilatation (compare with diameter of arch of aorta). LPA—left pulmonary artery. LPV—left pulmonary vein. AL—left auricle. RV—right ventricle. (a)—site from which section shown in figure 4 was prepared. (b)—flattened, discolored portion of left recurrent laryngeal nerve and site from which section shown in figure 5 was prepared. Note the relations of aortic arch, left pulmonary artery and ligamentum arteriosum to the nerve and the remoteness of the left auricle from the nerve.



FIG. 3. *Case 1.* Photograph of dissection. Posterior view. A—arch of aorta. LS—left subclavian artery. V—vagus nerve. LRN—left recurrent laryngeal nerve. E—retracted esophagus. LPA—left pulmonary artery. LB—left bronchus. RB—right bronchus. AL—left atrium. RP—cut edge of pericardium. (c)—site from which section shown in figure 6 was prepared. Note the relations of the aortic arch and left pulmonary artery to the nerve and the remoteness of left atrium from the nerve.

was made up of the right ventricle. There was considerable dilatation of both ventricles and some dilatation of the left atrium. The weight of the heart (with 2.5 cm. of the aorta and the pulmonary artery attached) was 530 gm. The left ventricular wall measured 14 mm. and the right ventricular wall measured 6 mm., each measurement being made midway between the base and the apex. There was thickening of the left atrial wall. The valve ring measurements were as follows: tricuspid 120 mm., pulmonary 80 mm., mitral 117 mm., and aortic 60 mm. Over a distance of about 3.5 cm. the anterior leaflet of the mitral valve was considerably thickened and its free edge was thickened, rolled and smooth. The attachments of the chordae tendineae to

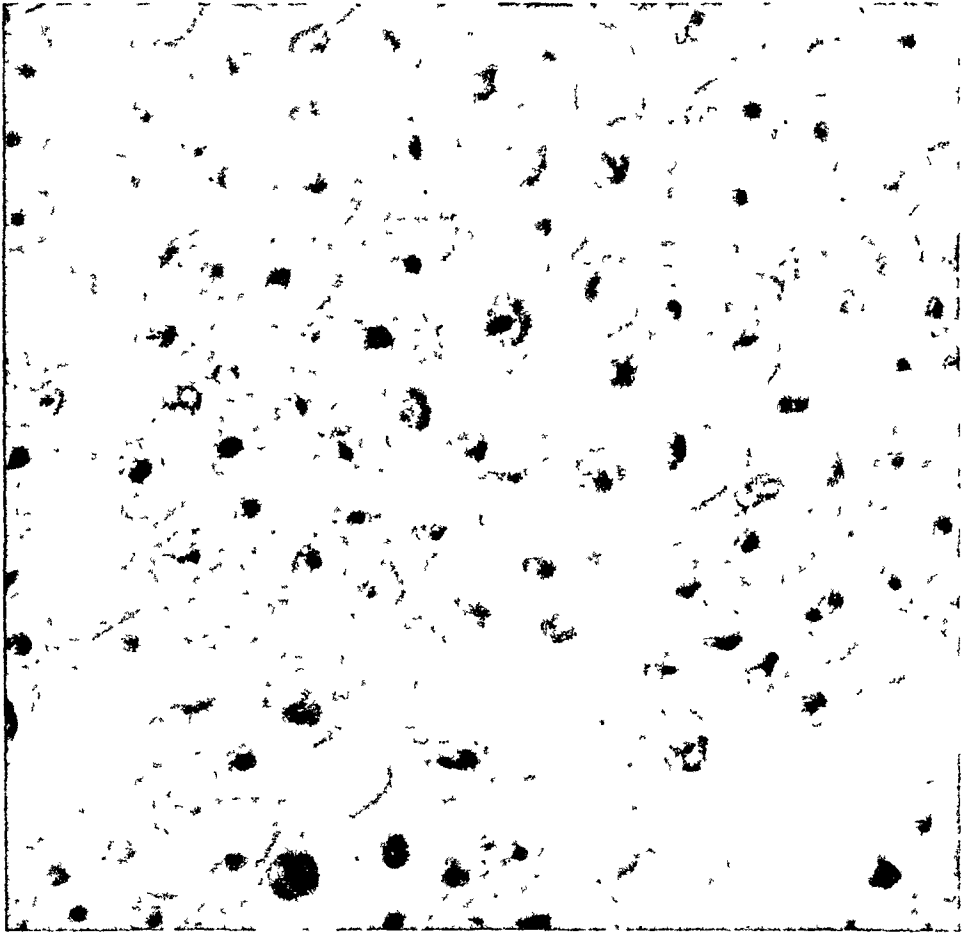


FIG. 4 *Case 1.* Photomicrograph of section of left recurrent laryngeal nerve from the proximal portion near the origin from the vagus (a in figure 2), Bodian's stain for axone cylinders. The axone cylinders are intact.

the mitral valve were thickened, shortened, distorted, nodular and matted together. On the surfaces of the thickened chordae tendineae at their attachments to the valve were very fine, dull, gray-pink nodules. Although the mitral valve was distorted, the degree of stenosis was minimal. The endocardium of the posterior wall of the left atrium, covering an area of about 4 by 5 cm., and directly above the attachment of the posterior cusp of the mitral valve, was dull, mottled gray, rough and traversed by fine, irregular ridges and depressions. The only abnormality noted in any of the coronary arteries was that of slight thickening in the proximal 3 cm. of

the left anterior descending branch. The gross appearance of the myocardium was normal. The pulmonary artery was dilated and there was a yellowish patch noted on the intima at the bifurcation.

Left recurrent laryngeal nerve: The relation of this nerve to the pulmonary artery, aortic arch, and ligamentum arteriosum was carefully determined (figures 2

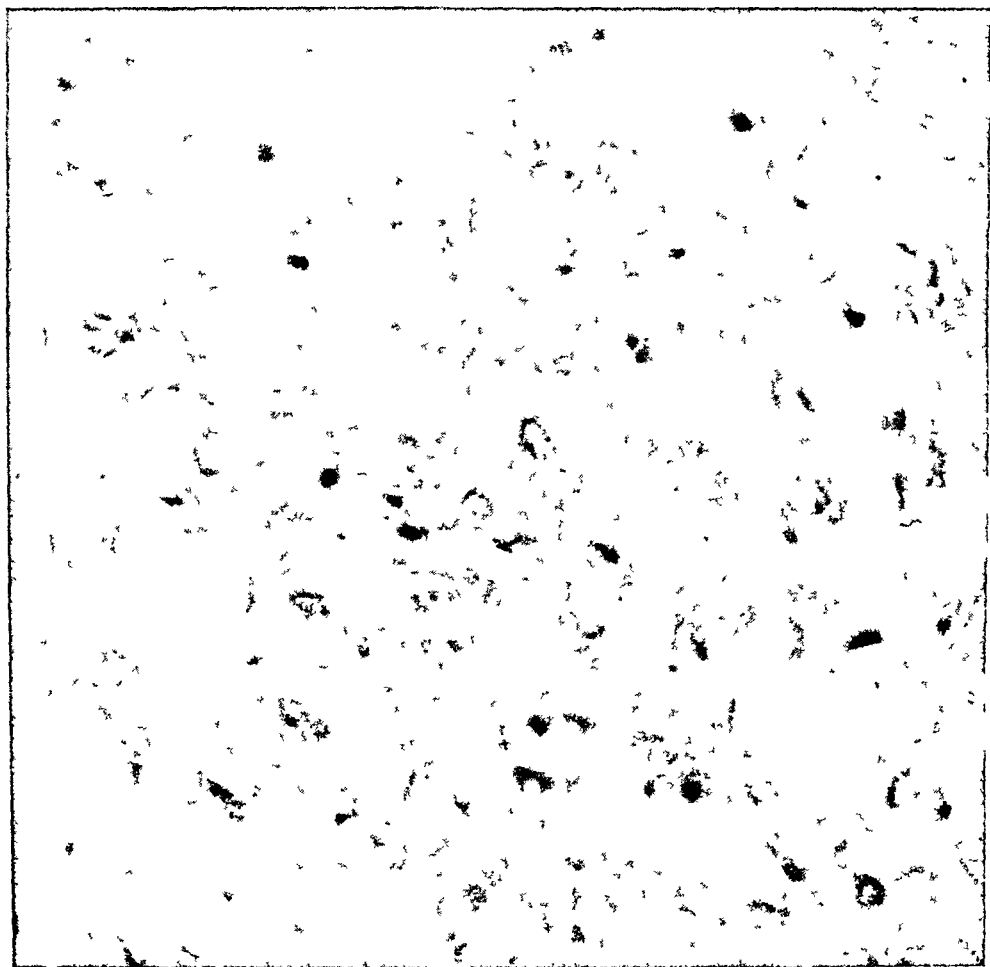


FIG 5 *Case 1.* Photomicrograph of section of left recurrent laryngeal nerve from the portion lying between the aortic arch and the left pulmonary artery (b in figure 2). Bodian's stain for axone cylinders. There is considerable degeneration of axone cylinders.

and 3). The nerve lay just lateral and in close apposition to the ligamentum arteriosum. The arch of the aorta was immediately superior, and the left pulmonary artery immediately inferior to it. The ligamentum arteriosum was 12 mm. long and 3 mm. wide; it was tough and about the same color and consistency as the adjacent aorta. The uppermost border of the left atrium was a considerable distance below the nerve and was separated from it by the left pulmonary artery and the left bronchus. The portion of the nerve between the left pulmonary artery and the arch of aorta was flattened and showed reddish brown discoloration.

Lungs and pleural cavities: There were approximately 200 c.c. of light brown fluid containing fibrin particles in the right pleural cavity and 300 c.c. of similar fluid in the left pleural cavity. The right lung was firmly adherent posteriorly to the thoracic cage. The external surface was purple-red, and there was no crepitation

anywhere in the lung. The cut surface of the right lung was dark purple-red, firm and moist throughout. The lateral portion of the left lung was firmly attached to the thoracic cage by adhesions. There was no crepitation in the upper lobe but some crepitation in the lower lobe. The cut surface of the left lung was firm and purple-red in the upper lobe and was bright red and wet in the lower lobe.

*Microscopic Observations.* Heart: A number of characteristic Aschoff bodies were present in the perivascular and interstitial tissues of all chambers and in the atrioventricular bundle. In addition, diffuse infiltrations of cells were present in the

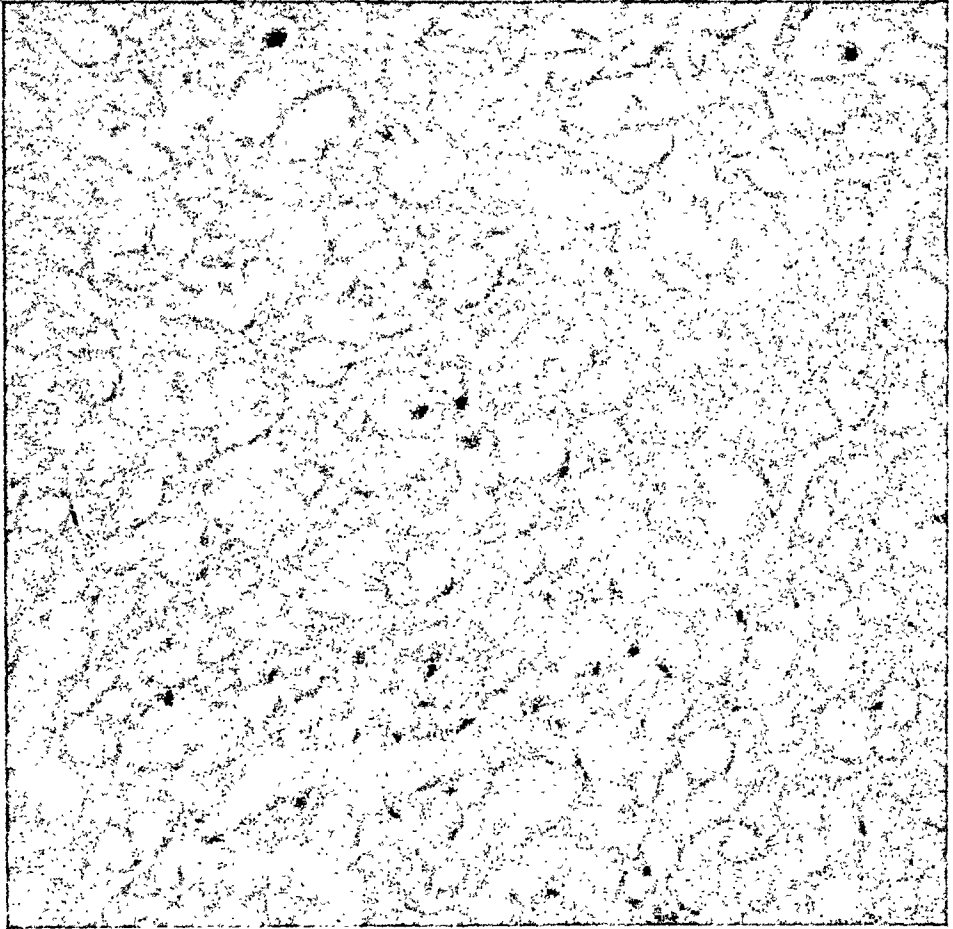


FIG. 6. *Case 1.* Photomicrograph of section of left recurrent laryngeal nerve from a portion of the nerve distal to that lying between aortic arch and left pulmonary artery (c in figure 3). Bodian's stain for axone cylinders. There is considerable degeneration of axone cylinders.

myocardium of all chambers, in the endocardium and epicardium of the left atrium, in the epicardial sheaths of the roots of the aorta and pulmonary artery, in the intima and media of the root of the aorta, in the mitral ring and mitral valve, and in the tricuspid ring and tricuspid valve. These cells were lymphocytes and larger mononuclear cells with irregular pyknotic and vesicular nuclei, some containing prominent nucleoli. In all chambers there were foci of necrosis of the myocardium. The endocardium of the left atrium was considerably thickened and edematous. Sections of the grossly distorted portion of the mitral valve revealed considerable thickening by fibrous connective tissue, edema, and vascularization.



Left recurrent laryngeal nerve: Sections from three levels of the left recurrent laryngeal nerve were prepared: (a) the proximal portion at its origin from the vagus, (b) the portion of nerve that lay between the left pulmonary artery and aorta, and (c) from a portion distal to that which lay between the pulmonary artery and the aorta. All three portions were processed simultaneously by Bodian's method,<sup>1</sup> a piece of normal spinal cord being used as a control. Sections of the control spinal cord revealed intact axones as did sections prepared from level (a) (figure 4). Those prepared from levels (b) and (c) revealed considerable degeneration of axones (figures 5 and 6).

Lungs: Many of the alveolar spaces were filled with red blood cells, a few lymphocytes, and polymorphonuclear leukocytes. In many alveoli there were also a number of macrophages with a great deal of brown granular pigment in the cytoplasm. The alveolar walls were considerably thickened and infiltrated with lymphocytes and large mononuclear cells with large, round and oval vesicular nuclei and distinct nucleoli. The capillaries in some regions were intensely congested. In the right upper lobe there was a sub-pleural accumulation of cells which resembled an Aschoff body. The walls of some of the pulmonary arterioles were considerably thickened, stained diffusely eosinophilic and contained few nuclei.

Anatomic Diagnosis: (1) Rheumatic valvulitis of the mitral valve with fibrosis and deformity; rheumatic valvulitis of the tricuspid valve; rheumatic mural endocarditis of the left atrium; hypertrophy of the myocardium of all chambers; (2) Hemorrhagic and interstitial pneumonitis; fibrous pleuritis of both lungs.

Comment: The clinical and pathological features of the pneumonitis resembled those that have been described in pneumonitis associated with active rheumatic fever. It was believed that the pneumonitis was a manifestation of an acute rheumatic state which precipitated the terminal event in this case.

Case 2. H. F. E., age 31, was admitted to the hospital complaining of hoarseness of three months' duration. The past history revealed that he had been discharged from the military service because of "valvular heart disease." Pertinent physical

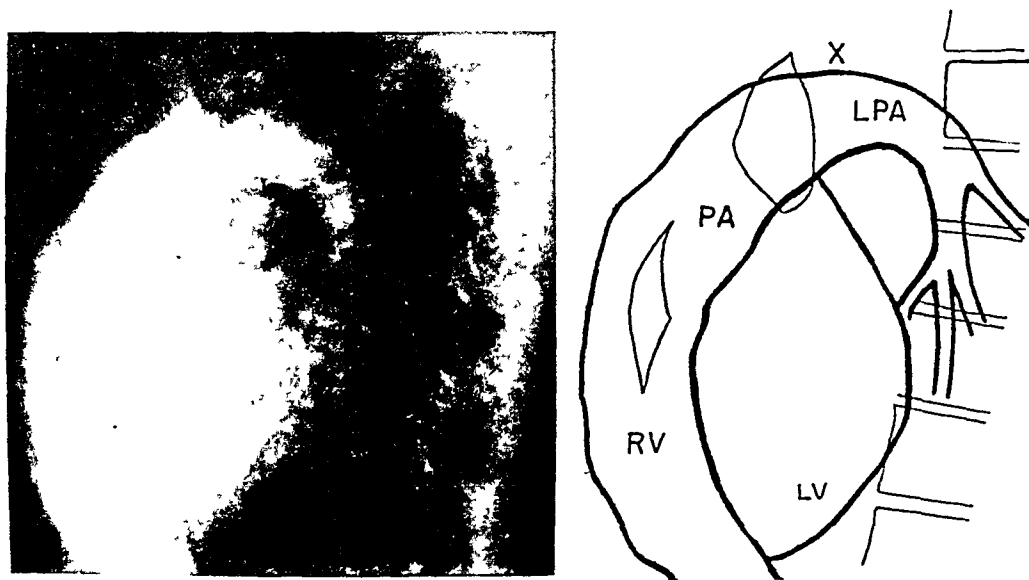


FIG. 7. Case 2. Angiocardiogram 3 sec. after injection of 70 per cent diodrast into arm vein. Left oblique view. PA—main stem of pulmonary artery. LPA—left pulmonary artery. RV—right ventricle. LV—left ventricle. The main stem and left branch of the pulmonary artery are dilated. The right ventricle is elongated. X—approximate location of left recurrent laryngeal nerve

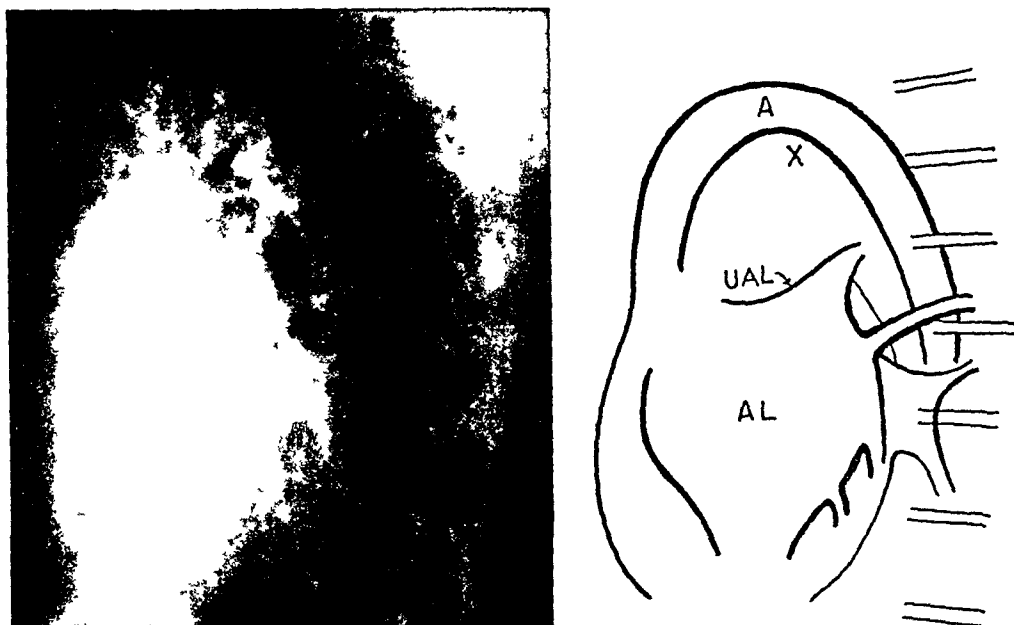


FIG. 8. *Case 2.* Angiocardiogram 11 sec. after injection of 70 per cent diodrast into arm vein. Left oblique view. A—arch of aorta. AL—left atrium. UAL—upper border of left atrium. X—approximate location of left recurrent laryngeal nerve.

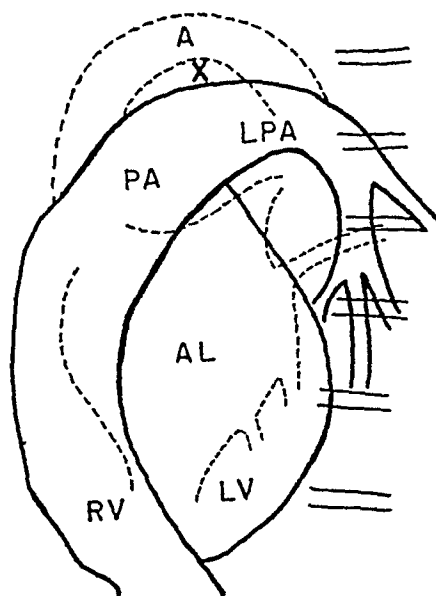


FIG. 9. *Case 2.* Diagram of superposition of angiocardiograms illustrated in figures 7 and 8. Labeling as in figures 7 and 8. Solid lines—diagram of angiocardiogram shown in figure 7. Dotted lines—diagram of angiocardiogram shown in figure 8.

findings were as follows: There was moderate left ventricular enlargement downward and to the left; an apical diastolic murmur was evident with an associated harsh mitral systolic murmur; the blood pressure was 90 systolic and 50 diastolic in each arm. The lung fields were clear. Laryngoscopic examination revealed flaccid paralysis of the left vocal cord. Roentgen-ray examination of the chest revealed the

cardiac silhouette to be of typical mitral configuration with enlargement in all diameters, particularly the longitudinal and oblique measurements. Esophageal compression was noted when barium swallow was given. The electrocardiogram revealed prolonged atrioventricular conduction (.23 sec.) as the only significant abnormality. Angiocardiograms (figures 7, 8 and 9) were done by Dr. George P. Robb, and his report is as follows: "The pulmonary valve and the main pulmonary artery are pushed cephalad toward the aortic arch by the elongated outflow tract of the right ventricle. The main stem of the pulmonary artery is enlarged throughout and measures 4.0 cm. in diameter (normal 3.0 cm.). At the bifurcation the diameter is still 4.0 cm. The left pulmonary artery as it passes beneath the aortic arch is also enlarged and measures 3.4 cm. in diameter. By superimposition of films the superior wall of the elevated and dilated left pulmonary artery seems to be in close contact with the overlying arch of aorta. The left atrium is enlarged in all diameters and extends to the right in the left anterior oblique view, displacing and compressing the superior vena cava and right auricular appendage. It is approximately 8.0 cm. in transverse and vertical diameters as compared to the normal values of 4.0 and 4.5 cm. Its concave upper border is far removed from the aortic arch by a distance of 3.5 cm. The thoracic aorta is poorly outlined because of two factors, the low concentration of diodrast in its lumen and the shadows of adjacent and overlying pulmonary veins. It is definitely small with a maximal transverse diameter of 2.5 cm. There is no evident displacement or distortion of the arch by the enlarged pulmonary artery or left branch."

### DISCUSSION

Left recurrent laryngeal nerve paralysis occurs very infrequently in heart disease. Fetterolf and Norris<sup>2</sup> who were particularly interested in this question encountered only one case among several hundred patients with cardiac disease. Reiche<sup>3</sup> noted only two cases among 300 patients with mitral stenosis. From a different point of view Scheifley and Smith<sup>4</sup> determined the incidence of mitral stenosis in a series of 223 cases of recurrent laryngeal nerve paralysis and found only 10 patients with mitral stenosis whereas New and Childrey<sup>5</sup> found only seven patients with mitral stenosis in a series of 322 cases of recurrent laryngeal nerve paralysis. Because of the infrequency with which heart disease is associated with recurrent laryngeal nerve paralysis it has been suggested that the association is purely coincidental.<sup>6</sup> This suggestion acquires some force from the fact that a large proportion of cases of recurrent laryngeal nerve paralysis is etiologically unexplained even after thorough study. Thus 33 per cent of the cases studied in one group<sup>5</sup> and 41 per cent of the cases studied in another<sup>4</sup> fell into this unexplained category. It is evident that if heart disease should occur by chance with these unexplained cases, an etiological relationship would be assumed. Nevertheless, the incidence of mitral stenosis is 10 times as great in patients with recurrent laryngeal nerve paralysis as in general hospital patients.<sup>4</sup> Furthermore, if the association were purely coincidental there should be no difference in the incidence of rheumatic heart disease among cases of left and right recurrent laryngeal nerve paralysis. Yet Scheifley and Smith<sup>4</sup> as well as New and Childrey<sup>5</sup> found all the cases of rheumatic heart disease associated with left recurrent laryngeal nerve paralysis and none associated with right recurrent laryngeal nerve paralysis.

This is what should be expected from an anatomical etiological association in view of the intimate anatomical relationship of the heart to the left recurrent laryngeal nerve, and its relative remoteness from the right recurrent laryngeal nerve. In the older literature there are some reports of right recurrent laryngeal nerve paralysis with rheumatic heart disease, but Fetterolf and Norris<sup>2</sup> found from a study of the literature that these were cases in which the left recurrent laryngeal nerve was also involved. Furthermore, they found no cases in which postmortem evidence was presented.

It may be accepted as established that the left recurrent laryngeal nerve is paralyzed in some way as a direct result of the heart disease. The explanations of the pathogenesis, however, have been varied. A common explanation of some of the older authors, and one which still is prevalent, was that the enlarged left atrium of mitral stenosis compressed the nerve. As long ago as 1911, however, Fetterolf and Norris<sup>2</sup> showed that it was next to impossible for the left atrium to impinge directly on the nerve. They pointed out that the nerve must be compressed between the aortic arch and the left pulmonary artery, and they believed that any condition which would dilate or force upward the left pulmonary artery, the left pulmonary vein or the left atrium would tend to produce nerve compression. These authors noted that some of the postmortem studies in the literature mentioned the obliterated ligamentum arteriosum, but they considered this of negligible importance. In those cases associated with a patent ductus arteriosus, the authors considered the important factor to be the resulting pulmonary artery dilatation. They believed that other explanations were either disproved by their anatomical studies or ill-founded. These other explanations included (1) traction on the ligamentum arteriosum and the nerve as a result of hypertrophy of the right ventricle and change in cardiac position, (2) compression of the nerve between a patent ductus arteriosus and the aortic arch, (3) compression of the nerve by peribronchial and peritracheal glands, enlarged as a result of congestive heart failure and (4) compression of the nerve between the left bronchus and the enlarged left atrium.

Notkin<sup>7</sup> reported a case with pulmonary artery dilatation in which he believed a lymph gland in the triangle formed by the aortic arch, the pulmonary artery and the ligamentum arteriosum contributed to compression of the nerve. He reviewed the literature up to 1924 and found only 17 cases with postmortem study. He concluded that the most important factor in the causation of the paralysis was either pulmonary artery dilation or pressure transmitted to the pulmonary artery by a dilated left atrium. He pointed out, however, that certain secondary factors might contribute to compression of the nerve such as thrombi in the left atrium, thrombosis of the pulmonary artery, arteriosclerosis of the pulmonary artery and aorta, and enlarged mediastinal glands. In a certain number of cases he believed that an initial neuritis occurred which was aggravated as the cardiac condition grew worse and which went on to degeneration as the nerve became compressed.

We are able to find only five case reports with postmortem study of rheumatic heart disease and left recurrent laryngeal nerve paralysis published since Notkin's<sup>7</sup> review. Klein<sup>8</sup> found mitral insufficiency rather than stenosis in his case with adhesive pericarditis at the base of the heart in the neighborhood of left atrium, aorta, and pulmonary artery. He believed that the pericarditis fixed the left atrium, preventing its usual posterior extension during enlargement and causing upward extension with pressure on the nerve through the displaced left bronchus. Reiche<sup>3</sup> found the pulmonary artery compressed and pushed aside by a greatly dilated left atrium which was filled with thrombi and which adhered to the aorta and the nerve. In Langeron's<sup>9</sup> case there was a Horner's syndrome as well as hoarseness. The left recurrent laryngeal nerve was embedded in dense scar tissue which also matted together all the other structures of the left side of the chest and was presumably due to healed mediastinitis. Alpert<sup>10</sup> found enormous dilatation of the pulmonary artery and its major branches and no enlargement of the left atrium. Eizaguirre<sup>11</sup> found a dilated left atrium filled with a large thrombus and a dilated pulmonary artery. He found the left recurrent laryngeal nerve compressed between the pulmonary artery and the aortic arch and believed that the large left atrium pushed the pulmonary artery against the aorta.

In 1934 King, Hitzig and Fishberg<sup>12</sup> reported three cases in which left recurrent laryngeal nerve paralysis was associated with congestive failure due to coronary arteriosclerotic heart disease. There was no rheumatic valvular disease in these cases. (Up to the time of this study almost all the reported cases had dealt with rheumatic heart disease and almost all of these with mitral stenosis.) In two of the cases postmortem studies were carried out. The authors attributed the nerve paralysis to compression by a dilated pulmonary artery, the latter being a consequence of the pulmonary hypertension resulting from left heart failure. They believed that the pulmonary artery dilatation was the important common factor in the cases of coronary arteriosclerotic heart disease with failure and rheumatic heart disease. They pointed out that the pulmonary artery dilatation might be dynamic rather than structural and that there might be little or no postmortem evidence.

Other forms of cardiac abnormality with pulmonary artery dilatation and left recurrent laryngeal nerve paralysis have been reported. These included interatrial septal defect<sup>7, 13, 14, 15</sup> and the Eisenmenger syndrome.<sup>16, 17</sup> The left atrium was not described in some of these reports, but where it was noted it was not enlarged, or enlarged only slightly.<sup>13, 15</sup>

In Case 1 of this report there was roentgenographic and postmortem evidence of pulmonary artery dilatation (figures 1 and 2) whereas in Case 2 the pulmonary artery dilatation was demonstrated by angiocardiograms (figures 7 and 9). The left atrial enlargement was slight in Case 1 and more pronounced in Case 2. The gross dissections in Case 1 showed that the portion of the nerve lying between the aortic arch and the pulmonary

artery was discolored reddish brown and flattened. The discoloration may be significant but flattening of the nerve has been observed in normal cases.<sup>2</sup> The dissection showed further that while the nerve could readily have been compressed between the left pulmonary artery and the arch of the aorta, it was quite remote from any contact with the left atrium (figures 2 and 3). None of the other possible causes of nerve compression mentioned in the literature and discussed above were present. The histologic studies of the nerve localized the site of compression quite clearly as being between the left pulmonary artery and the arch of the aorta. It is interesting to note that there was no significant stenosis of the mitral valve.

The preponderance of evidence seems to indicate that pulmonary artery dilatation is the primary cause of the left recurrent laryngeal nerve paralysis. While this was a common factor in most of the cases studied, including our own, other factors may or may not have been present. Whether or not left atrial enlargement plays a contributory rôle in some cases (by pushing the left pulmonary artery against the aorta), as some authors have suggested, is difficult to demonstrate. The fact that the paralysis has been observed in cases in which there was no significant left atrial enlargement would tend to minimize the importance of this factor. It cannot be denied that in certain cases other factors may be involved in addition to pulmonary artery dilatation; these have already been mentioned in the review of the literature.

It is a very puzzling fact that while pulmonary artery dilatation is common, associated left recurrent laryngeal nerve paralysis is rare. King, Hitzig and Fishberg<sup>12</sup> attempted to explain this discrepancy by the relation of the ligamentum arteriosum to the nerve. They believed that if the ligamentum is so situated as to fix the nerve, and keep it from slipping as the pulmonary artery dilates, it should favor compression of the nerve in the triangle formed by the arch of the aorta, the ligamentum arteriosum and the left pulmonary artery. These authors postulated that such an anatomical relationship is rare. Jetterolf and Norris,<sup>2</sup> on the contrary, indicated that such a relationship is usual. Their sections and dissections were carried out in cadavers pre-hardened by arterial injection of formalin thus preserving the original relations as well as possible. The essence of their description was as follows: The left recurrent laryngeal nerve hugs the aorta closely and passes under the arch either at the point at which the ligamentum arteriosum joins the latter or slightly anterior to this position. The ligamentum arteriosum is a fibrous cord, about 3 mm. thick and 2 cm. long, lies almost exactly in the anteroposterior plane of the body and ascends but slightly as it passes backward from the left pulmonary artery to the aorta. In or slightly anterior to the obtuse angle formed at its junction with the latter vessel lies the recurrent laryngeal nerve. The left branch of the pulmonary artery passes outward and markedly backward. Above and 4 mm. away from it is the beginning of the descending part of the aorta to which it is connected by the ligamentum arteriosum. The normal relations, then, seem

to provide quite well the conditions for compression of the nerve in the triangle formed by the aortic arch, the ligamentum arteriosum, and the left pulmonary artery. It would not seem to require much pulmonary artery dilatation to fix the nerve against the ligamentum arteriosum and permit compression between pulmonary artery and aorta. Why this does not occur more frequently cannot be explained at present. It is possible that there is individual variation in susceptibility of the nerve to pressure, and that in most instances the nerve withstands pressure from a dilated pulmonary artery without functional derangement.

### SUMMARY

Two cases of rheumatic heart disease associated with left recurrent laryngeal nerve paralysis are reported. Angiocardiographic studies were carried out in one case and postmortem studies in the other. The literature is briefly reviewed, and the cause of the paralysis is discussed. The primary factor is compression of the nerve by dilatation of the left pulmonary artery. In view of the relative frequency of pulmonary artery dilatation, however, the rarity of left recurrent laryngeal nerve paralysis remains unexplained.

### BIBLIOGRAPHY

1. MALLORY, F. B.: Pathological technique, 1944, W. B. Saunders Co., Philadelphia, Pa., p. 228.
2. FETTEROLF, G., and NORRIS, G. W.: The anatomical explanation of the paralysis of the left recurrent laryngeal nerve found in certain cases of mitral stenosis, *Am. Jr. Med. Sci.*, 1911, cxli, 625.
3. REICHE, F.: Linksseitige Rekurrenslähmung bei Mitralstenose, *Med. Klin.*, 1926, xxii, 1142.
4. SCHEIFLEY, C. H., and SMITH, H. L.: Mitral stenosis and paralysis of the left recurrent laryngeal nerve, *Minnesota Med.*, 1942, xxv, 362.
5. NEW, G. B., and CHILDREY, J. H.: Paralysis of the vocal cords. A study of 217 medical cases, *Arch. Otolaryng.*, 1932, xvi, 143.
6. KELLY, A. B.: Neurological and mechanical factors underlying immobility of the vocal cords. I. The neurological aspect, *Brit. Med. Jr.*, 1927, ii, 678.
7. NOTKIN, M.: Paralysis of the left recurrent laryngeal nerve in mitral stenosis, *Arch. Int. Med.*, 1924, xxxiii, 71.
8. KLEIN, F.: Über einen Fall von Linksseitiger Rekurrenslähmung bei einem Mitralvitium, *Med. Klin.*, 1922, xviii, 76.
9. LANGERON, L.: Rétrécissement mitral—paralysie récurrentielle—syndrome de Claude Bernard-Horner, *Bruxelles-med.*, 1928, ix, 163.
10. ALPERT, S.: Recurrent laryngeal nerve palsy in mitral stenosis, *Am. Heart Jr.*, 1943, xxv, 689.
11. EIZAGUIRRE, L.: Estrechez mitral con signo de Ortner, *Med. iberica*, 1935, i, 465.
12. KING, F. H., HITZIG, W. M., and FISHBERG, A. M.: Recurrent laryngeal paralysis in left ventricular failure, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 691.
13. HOTZ, A.: Über angeborene Trikuspidinsuffizienz, *Jahrb. f. Kinderheilk.*, 1923, cii, 1.

14. WAHL, H. A., and GARD, R. L.: Aneurysm of the pulmonary artery, Surg., Gynec. and Obst., 1931, lii, 1129.
  15. ERLANGER, H., and LEVINE, S. A.: Atrial septal defect. A report of two cases in which there was recurrent laryngeal nerve paralysis, Am. Heart Jr., 1943, xxvi, 520.
  16. BAUMGARTNER, E. A., and ABBOTT, M. E.: Interventricular septal defect with dextro-position of aorta and dilatation of the pulmonary artery ("Eisenmenger complex") terminating by cerebral abscess, Am. Jr. Med. Sci., 1929, clxxvii, 639.
  17. TALLEY, J. E.: Tetralogy of Fallot (Eisenmenger type) with hypoplasia of the dextro-posed aorta, Am. Jr. Med. Sci., 1936, cxc, 618.
- .



# STUDIES ON VENOUS PRESSURE IN HEPATIC CIRRHOSIS\*

By LOUIS K. LEVY, M.D., and GEORGE E. BURCH, M.D., F.A.C.P.,  
*New Orleans, Louisiana*

This work was undertaken to evaluate venous pressure measurements in diagnosis of cirrhosis of the liver. Only patients with classical clinical manifestations of cirrhosis were included in these studies. It is interesting that no study of pressure in the veins of the collateral circulation of the liver could be found in the medical literature.

Ten normal white subjects and 10 white subjects with cirrhosis, ranging in age from 23 to 81 years, were observed (tables 1 and 2). Measurements

TABLE I

Pressure within the Veins of the Antecubitus Region, Abdomen and Dorsum of the Feet of 10 Normal White Women Resting Supine

Subject No.	Age in Years	Vein				
		Antecubital	Abdominal		Pedal	
			Right	Left	Right	Left
1	67	95	105	110	120	125
2	25	125	160	135	100	110
3	27	100	100	115	105	100
4	40	65	100	115	85	90
5	31	105	110	100	125	130
6	40	115	135	120	125	120
7	30	95	140	135	100	115
8	24	120	130	110	110	100
9	26	110	120	110	130	120
10	23	100	85	70	120	130
Max.		125	160	135	130	130
Min.		65	85	70	85	90
Mean		103	119	112	112	114

were obtained with the subjects in the supine position and with the use of apparatus described in earlier publications.<sup>1, 2</sup> The antecubital veins, the superficial abdominal (thoracoepigastric, superficial epigastric and superficial circumflex iliac) group of veins and the veins of the dorsal venous rete of the feet were the sites of study. Determinations were obtained just prior to and immediately following paracentesis. At all times measurements were

\* Received for publication January 31, 1948.

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans.

Aided by grants from the Life Insurance Medical Research Fund, A War Contract No. WD-49-007-MD-389, Helis Institute for Medical Research, and the Mrs. E. J. Caire Fund for Research in Heart Disease.

TABLE II

Pressure within the Veins of the Antecubitus, Abdomen and Dorsum of the Feet of 10 Patients with Classical Hepatic Cirrhosis  
(a) Before Paracentesis

Subject No.	Sex	Age in Years	Vein				
			Antecubital	Abdominal		Pedal	
				Right	Left	Right	Left
11	F	81	120	240	225	195	190
12	M	58	140	210	205	160	170
13	M	62	65	110	100	100	110
14	M	52	80	65	90	180	170
15	M	47	85	75	80	60	75
16	M	55	95	220	180	130	125
17	M	46	110	130	140	120	130
18	M	54	105	110	100	115	130
19	F	40	40	130	130	115	100
20	M	48	85	115	125	115	100
Max.			140	240	225	195	190
Min.			40	65	80	60	75
Mean			93	141	138	129	130

(b) After Paracentesis

Subject No.	Vein					Quantity, Liters
	Antecubital	Abdominal		Pedal		
		Right	Left	Right	Left	
11	110	165	155	125	130	8.8
12	120	160	160	125	135	3.2
13	65	100	85	95	90	3.6
14	80	25	40	60	50	14.3
15	85	85	90	115	110	3.0
16	90	200	170	110	120	2.8
17	100	90	100	110	120	9.0
18	110	95	90	115	120	1.5
19	45	90	95	110	105	1.0
20	90	100	110	110	105	5.4
Max.	120	165	170	125	135	
Min.	45	25	40	60	50	
Mean	90	111	110	108	109	

made at the phlebostatic axis and level. The quantity of ascitic fluid removed varied considerably, the minimum being one liter and the maximum 14.3 liters (figure 1).

Analysis of results showed a wide range of variations in the values for venous pressure, with overlapping of the values for normal and abnormal subjects. The average pressure in the abdominal and pedal veins of the cirrhotic group tended to be greater before paracentesis than in the normal subjects (table 2 and figure 1). There was a consistent, though slight,

decrease in the pressure in the abdominal veins after paracentesis. There were no uniform changes in the pressure in the antecubital and pedal veins following removal of ascitic fluid, although the pressure within the veins of the foot usually decreased (table 2 and figure 1). Individual variations for the normal subjects are shown in table 1. These are in agreement with values previously reported.<sup>3</sup>

#### VENOUS PRESSURE IN HEPATIC CIRRHOSIS

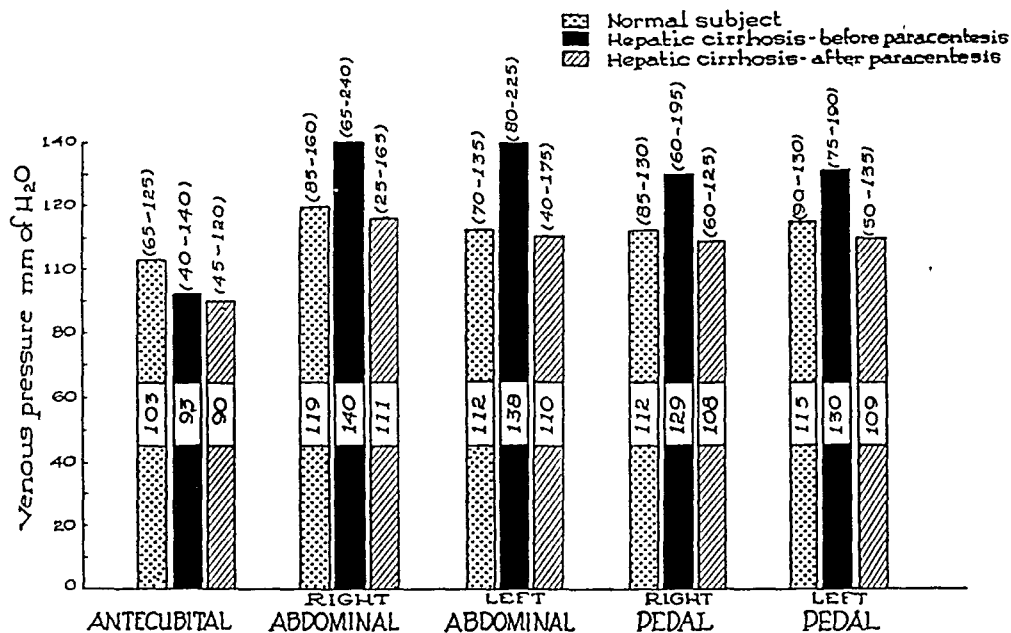


FIG. 1.

Patient numbers 11, 12, 17 and 19 experienced a decided drop in venous pressure, especially in the abdominal and pedal veins, following removal of 8.8, 3.2 and 1 liters of ascitic fluid respectively. However, in patient numbers 17 and 19 the pressure in the veins of the abdomen and feet was reduced to within normal range following paracentesis. Patient number 13, who had approximately the same amount of fluid removed as patient number 12, presented no initial elevation of venous pressure and no change following paracentesis. Patient number 14 exhibited a considerable fall in venous pressure in the veins of the abdomen and feet following paracentesis, even though initial pressures in the abdominal veins did not exceed the normal range. Patient numbers 16, 18, and 20 showed no appreciable change in venous pressure following removal of ascitic fluid.

Some of the subjects revealed a decrease in pressure in the veins of the abdomen and feet following paracentesis, the final pressures remaining elevated, as might be anticipated, since there is obstruction to flow in the portal vein in hepatic cirrhosis. However, results were too inconsistent to permit the use of venous pressure determinations as reliable diagnostic evidence in

suspected cases of hepatic cirrhosis. The changes in pressure following paracentesis were sufficient to demonstrate the value of this procedure in improving the hemodynamics of the venous circulation below the level of the diaphragm. Failure of the pressure to rise in the abdominal veins in some of the patients with hepatic cirrhosis indicates lack of overloading and adequacy of the parahepatic collateral circulation. It is possible that the entrance of the portal venous blood to the collateral vessels may be incomplete, even though these vessels can drain the blood adequately. The ascites in these patients is most probably related to factors other than venous hypertension of the portal system.

#### BIBLIOGRAPHY

1. BURCH, G. E., and SODEMAN, W. A.: A direct method for the measurement of venous pressure: Relationship of tissue pressure to venous pressure, *Jr. Clin. Invest.*, 1939, xviii, 31.
2. BURCH, G. E., and WINSOR, T.: The phlebomanometer, a new apparatus for direct measurement of venous pressure in large and small veins, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 91.
3. WINSOR, T., and BURCH, G. E.: Use of the phlebomanometer: normal venous pressure values and a study of certain clinical aspects of venous hypertension in man, *Am. Heart Jr.*, 1946, iii, 387.

# ACUTE MERCURY POISONING: TREATMENT WITH BAL AND IN ANURIC STATES WITH CONTINUOUS PERITONEAL LAVAGE\*

By RANDOLPH BATSON, M.D., and J. CYRIL PETERSON, M.D.,  
*Nashville, Tennessee*

THE past 30 years have seen the introduction of a number of schemes for the treatment of acute bichloride of mercury poisoning. Until recently, none of them has proved to be generally effective in preventing death in severe cases.

BAL (2, 3-dimercaptopropanol) has been found to be an effective antidote for mercury poisoning. Peritoneal lavage as recently improved is a satisfactory procedure for the treatment of temporary anuric states. These advances make possible the formulation of a therapeutic regime which should enable us to save most of the patients who ingest and retain fatal doses of mercuric salts—even those seen too late for proper antidotal treatment.

We have recently had an opportunity to observe modern therapy in such a patient and believe that the experience will serve as the basis for formulating a general therapeutic plan.

## GENERAL CONSIDERATIONS

A number of factors are of significance in the consideration of cases of mercury poisoning. The foremost of these is the dose of the salt ingested and retained. Experimental animals do not survive when 4 mg. per kilogram is given intravenously or when, with the prevention of vomiting, 30 mg. per kilogram is given orally. In man, vomiting follows the ingestion of mercury bichloride with such regularity that it has served to separate real from spurious cases. The effect of the salt is to a large extent modified by the early onset of emesis; however, it is generally believed that the ingestion of 1 gram regularly results in serious poisoning<sup>1, 2, 3, 4, 5</sup> and that 1.5 grams will commonly lead to a fatal termination.<sup>6</sup>

For various reasons only about half of the patients who appear at a hospital with a history of bichloride of mercury ingestion develop significant symptoms of poisoning and of the half who develop symptoms half, or 25 per cent of the whole group, fail to survive.<sup>5</sup> This makes it very difficult to interpret the results in small series of cases.

Bichloride of mercury is a simple protoplasmic poison which produces tissue necrosis whenever and wherever critical concentrations of the drug obtain. The principal pathological lesions are related to the sites by contact during absorption or by concentration in the excretory processes. The

\* Received for publication September 15, 1947.

From the Department of Pediatrics, Vanderbilt University School of Medicine.

earliest lesions are the direct result of the contact of the salt with the mucous membranes of the mouth, stomach and upper small intestine, or occasionally the vaginal mucous membranes. Absorption is rapid and in a very short time injurious concentrations occur in the renal tubules and in the colon where the drug is concentrated by excretion. Very large doses of the drug lead to death in a period of one to two days, primarily as a result of shock-like states. Of those who do not initially show this reaction there is a group of mild cases who may show little or no evidence of poisoning. Still another group, who usually have vomiting and diarrhea as early predominant symptoms, develop signs of renal damage, often in the form of anuria which may occur either early or late in the course of their illness.

Hull and Monte <sup>5</sup> have found that the prognosis is extremely grave when patients have a period of anuria lasting 24 hours or more or when they develop a blood nonprotein nitrogen level above 125 mg. per cent. Peters, Eisenman and Kydd <sup>4</sup> reported a mortality rate of 25 per cent in a series of cases in which all fatalities experienced a period of anuria and all survivors escaped even transitory anuria. Rosenbloom <sup>7</sup> in 1915 demonstrated that while mercury could be found in practically every tissue of the body in fatal cases, the most important lesion in serious cases surviving the immediate shock stage is the necrosis of the epithelium in the convoluted tubules of the kidney. Fortunately, the tubular epithelium of the kidney has remarkable powers of regeneration,<sup>4</sup> and healing may occur without residual impairment of renal function. For this reason, the treatment of patients with anuria should be directed toward the prevention of death due to retention of waste products until the tubular epithelium regenerates and renal function returns. This generality was well expressed and emphasized by Hayman and Priestley.<sup>8</sup>

#### PAST TREATMENT REGIMES

Lambert and Patterson <sup>9</sup> in 1915 presented a regime for the treatment of acute mercury poisoning which aimed at the prevention of the reabsorption of the excreted mercury. This plan involves gastric lavage, colonic irrigations, and the administration of large amounts of alkaline solutions and milk by mouth. Only two of their 16 cases so treated died. Weiss <sup>10</sup> in 1917 reported 25 cases which were apparently mild but were successfully treated by a modification of the above plan. Others have been unable to achieve equivalent results. Peters, Eisenman, and Kydd <sup>4</sup> strongly advocated measures aimed at the prevention of shock, dehydration and salt depletion. Although the mortality rate has not been greatly reduced by such measures, it is now generally accepted <sup>2, 3, 4, 8, 9, 11, 12, 5</sup> that every effort should be made to keep these patients, as near as possible, in a normal state of fluid and electrolytic balance.

Various drugs have been used to combat the poisoning from bichloride of mercury. These were usually employed on the principle of the therapeutic

agent combining with mercury to produce an excretable nontoxic substance. These were usually sulfur containing drugs, among which were calcium sulfide, hydrogen sulfide, sodium thiosulfate, and sodium formaldehyde sulfoxylate. The latter drug, which was introduced by Rosenthal,<sup>13</sup> is still being used rather widely with variable results. Hull and Monte,<sup>14</sup> who treated 40 patients with this drug, found the results no better than those obtained by other therapeutic measures. Muir, Stenhouse and Becker<sup>15</sup> could not protect rabbits from mercury poisoning by giving sulfur containing compounds after mercury poisoning. They did, however, demonstrate that some protection could be obtained when the therapeutic agents were given before the poisoning was produced. Mintz<sup>16</sup> in 1933 reviewed the literature on the treatment of acute mercury poisoning and stated, "in the interval before the local physician has arrived, which I feel is more than 13 minutes, the patient has either saved himself by early vomiting or else has absorbed the lethal dose, provided, of course, that a sufficient quantity has been taken."

Although a number of surgical procedures have been advanced for the treatment of the various lesions, none of them has been significantly effective. Anderson<sup>17</sup> and Berger, Applebaum and Young<sup>1</sup> tried colostomy with colonic irrigation. Mintz<sup>16</sup> expressed the opinion that their statistics were far from convincing and very aptly asked if high colonic irrigations could not accomplish the same purpose.

Renal decapsulation has been used for many years in the treatment of anuria, usually on the basis of relieving the pressure on the renal tubules. It is true that there are isolated reports of anuric patients who coincidentally or otherwise improved following this procedure. However, the unsuccessfully treated cases by far outnumbered the successes and it would seem, in general, the results do not justify renal decapsulation, especially in view of the trauma and shock associated with the procedure.

Johnstone<sup>18</sup> in 1931 successfully treated two patients with anuria secondary to mercury poisoning by venesection and multiple transfusions. Hashinger and Simon<sup>19</sup> in 1935 used "exsanguination" and multiple transfusions successfully in the treatment of a patient with a severe intoxication and uremia. This procedure may have been of considerable value prior to the use of BAL and peritoneal lavage.

#### RECENT ADVANCES IN THERAPY

BAL (2, 3-dimercaptopropanol) is a product of British war research; developed principally by Peters, Stocken and Thompson<sup>20</sup> to combat the toxic effects of arsenic. They believe that the arsenic in combining with a tissue -SH group inactivates an enzyme system vital to cellular metabolism. BAL combines with the arsenical and effectively prevents this cellular damage. These studies led to investigations of the effects of this drug on poisoning by other heavy metals.<sup>20, 21, 22, 23</sup> As a result of these studies proof now

exists that mercury also inactivates a cellular enzyme system and that these effects may be prevented by the administration of BAL. It seems probable from the above studies that while BAL is most effective when given early it may be of value even late in mercury poisoning. This has been borne out experimentally<sup>22, 23</sup> as well as clinically<sup>6</sup> and it seems very likely that BAL can reactivate enzyme systems already poisoned by mercury.<sup>23</sup>

Longcope and Luetscher<sup>6</sup> recently reported very dramatic results in BAL treatment of 42 patients who had ingested from .5 to 20 grams of bichloride of mercury. All but two of these patients survived. One exception, a patient who did not receive BAL until 13 hours had elapsed, died on the ninth day after poisoning. The other exception was a woman who had taken 2 grams of bichloride of mercury six hours before admission. These workers emphasized the great importance of therapy within the first few hours after the ingestion of mercury and the continuance of such therapy for several days thereafter. For a comparison they pointed out that before the use of BAL they had treated 86 patients by former methods within four hours of poisoning and that, of these, 27 had died. Of the 24 patients in the BAL treated series, who received therapy within 4 hours, there were no deaths. These authors employed an initial intramuscular injection of 300 mg. of BAL followed within the first 12 hours by two or three additional injections of 150 mg. each. During the second 12-hour period their patients usually received one and often two 150 mg. injections after which time they were usually given two injections of 150 mg. each day for one to two days, depending on the condition and response of the patient. Their patients received a total of between 1200 and 2870 mg.

As a result of the above experimental and clinical studies, it seems highly probable that a really effective antidote for acute mercury poisoning has been found. The prognosis is apparently good provided the patient is treated within the first four hours, even following the ingestion of relatively large amounts of bichloride.

There still remains a group of these patients who, not having received BAL therapy within the first few hours, will develop anuria secondary to tubular injury. These patients will ultimately die unless something can be done to provide a temporary means of controlling their uremia until renal function returns.

For many years it has been known that the organic solutes and electrolytes in plasma would dialyze across the peritoneal membrane.<sup>24</sup> Bliss showed that the lives of rabbits, made anuric with bichloride of mercury poisoning, could be prolonged and the mortality could be reduced by peritoneal irrigations. Prior to 1940, attempts to treat humans by peritoneal irrigations were unsatisfactory<sup>27, 28, 29</sup> because of inadequate control of electrolyte balance and inability to effectively treat the peritonitis that is so apt to develop.



In 1934, Balazs and Rosenak<sup>29</sup> attempted peritoneal irrigation in two patients with anuria secondary to mercury poisoning. Though their patients died, they temporarily prevented the development of azotemia. Their failure was probably due to the fact that a simple glucose solution was used for the irrigations and the periods were far too brief.

Recently two separate groups of workers have revived interest in this procedure and have done much to eliminate many of the hazards of peritoneal irrigations.

Abbott and Shea,<sup>30</sup> after animal experimentation, postulated that this procedure could be effectively employed in patients with anuria following bichloride of mercury poisoning, hemolytic transfusion reactions, toxic nephrosis due to sulfonamides, or developing as a part of the "crush syndrome." They studied solutions of varying composition for peritoneal lavage and came to the conclusion that a solution with a balanced salt mixture made slightly hypertonic with glucose was most effective. They found that waste products and "presumably other toxic elements," could be removed from the blood stream by intermittent peritoneal lavage and that their nephrectomized animals could be kept in a relatively normal state of fluid and electrolyte balance for a week or more.

Independently, Seligman, Frank and Fine<sup>31</sup> found that peritoneal lavage was 40 to 70 per cent as effective as normal kidney function and that nephrectomized dogs with uremia could be improved and could be kept alive 3 to 10 days. Their animals died of peritonitis but did not redevelop uremia while under treatment. They used a modified Tyrode's solution with heparin to prevent intraperitoneal fibrin deposition and penicillin and sulfadiazine as a prophylaxis against infection. They recommended 20 to 50 ml. per minute as the optimal rate of flow for maximum urea clearance. After the azotemia, which developed in pre-lavage period, was corrected, peritoneal irrigations for 8 to 10 hours each day prevented the reaccumulation of waste products.

Recently this group reported<sup>32</sup> the results of peritoneal irrigation in four patients. The first of these had azotemia secondary to an inoperable uterine carcinoma but was temporarily improved by the lavage. Attempts to control the uremia by other forms of dialysis had been ineffectual. The second, a 14 year old girl with anuria due to a hemolytic transfusion reaction, was successfully treated for the azotemia but subsequently died from pulmonary embolism. The third, a 51 year old man with anuria secondary to sulfonamide poisoning, was controlled by peritoneal lavage until the fourteenth day of anuria when his urinary function returned. The last, a 19 year old girl with anuria from a hemolytic transfusion reaction, died after her course was complicated by the development of shock and pulmonary edema.

They concluded from these experiences that it would be desirable to make the irrigating fluid hypertonic with 2 per cent dextrose to prevent the tendency to develop pulmonary edema, a complication encountered in three of the four cases.

## CASE REPORT

A 17 year old white female was admitted to the Pediatric Service of Vanderbilt Hospital\* on August 1, 1946, with anuria of five days' duration.

Five days prior to admission she took two .5 gram tablets of bichloride of mercury. Ten minutes later she developed severe nausea and vomiting and her mouth and throat became sore. She stated that she had vomited every time she took fluids or ate during these five days. She did not void after the ingestion of the mercuric salt.

Two days after the onset of anuria a physician was called to treat her sore throat. A diagnosis of diphtheria was made, confirmed by smear and culture, so she was given 40,000 units of diphtheria antitoxin intramuscularly. It was only after this lapse of time, four days, that she admitted taking the bichloride of mercury. Her physician recommended hospitalization when the anuria persisted another day.

Physical Examination: Temperature 99°, pulse 96, respirations 22, blood pressure 132/90. The patient was a tall, slender girl who lay quietly in bed, complaining occasionally of pain in her throat and abdomen. She was slightly but definitely lethargic. She was cooperative except during her bouts of vomiting when she screamed out with pain. She was moderately dehydrated rather than edematous and there was evidence of recent weight loss. Her buccal mucosa showed several 1 by 1 cm. ulcerated areas covered by a soft gray membrane and surrounded by an area of redness approximately 1 cm. in width. The tonsils were enlarged and covered by a similar membrane and the posterior pharynx showed extreme redness with several large ulcerated areas. The cervical lymph nodes were moderately enlarged and tender. The heart was normal in size and sounds with a rate of 80 to 100 beats per minute and the electrocardiograms showed no abnormalities. The lungs were clear. There was generalized abdominal tenderness.

Admission laboratory studies showed: red blood cells 2.89 million, hemoglobin 10.5 gm., and white blood cells 27,700; bleeding time, coagulation time and clot retraction time were within normal limits. The blood non-protein nitrogen was 203 mg. per cent, plasma CO<sub>2</sub> combining power 32.4 volumes per cent, plasma chloride 72.9 milliequivalents per liter and plasma phosphorus 14.8 mg. per cent. Catheterization yielded approximately 30 c.c. of very thick, cloudy, mucoid material having no resemblance to urine.

The patient was immediately (on the fifth day) started on BAL therapy, receiving 225 mg. every four hours for 14 doses, 3.15 grams in 56 hours. The dosage was then reduced to 225 mg. twice daily and was continued until the end of the seventeenth day to a total of 7 grams.

Because of secondary infection of her pharyngeal lesions, she was given 15,000 units of penicillin every four hours and, in varying dosage, this antibiotic was continued for 35 days.

For the prevention of excessive edema parenteral fluids were limited. Attempts to administer fluids by mouth were unsuccessful because of continued nausea and vomiting. She was given 50 per cent dextrose intravenously on several occasions in a futile attempt to establish diuresis.

After the sixth and seventh days it was apparent that the patient was getting much worse. Complete anuria continued while lethargy became more marked. Her plasma chloride level and CO<sub>2</sub> combining power remained essentially unchanged, but her blood nonprotein nitrogen level had risen to 240 mg. per cent. It was felt that she could not possibly survive unless her uremia could be temporarily controlled and, with this in mind, continuous peritoneal lavage was initiated.

Under local anesthesia and with the patient in bed, an incision was made below and parallel to the right costal margin and a No. 24 mushroom catheter was inserted.

\* Admission to the Pediatric Service was due to the misrepresentation of her age.



FIG. 1. Photograph of peritoneal inflow and outflow tubes in place.

The tissues were closed snugly about the catheter with fine interrupted silk sutures. Another incision approximately  $\frac{1}{2}$  inch in length was made just medial to the left anterosuperior crest of the ilium and a rather large paracentesis trocar was pushed through the peritoneum. The trocar was withdrawn from its casing and replaced by a closely fitting suction tip. A similar closure was made here. Peritoneal irrigation was initiated with 1 liter of solution per hour being allowed to flow by gravity through the mushroom catheter, over the peritoneal surfaces, and out of the outlet tube in the left lower quadrant (figures 1 and 2).

TABLE I  
Peritoneal Irrigation Fluid\*  
(Solute in gm. per liter water)

Sodium chloride.....	6.10
Calcium chloride.....	0.23
Potassium chloride.....	0.35
Sodium phosphate (monobasic).....	0.07
Magnesium chloride.....	0.05
Sodium bicarbonate.....	2.20
Dextrose†.....	30-50
Penicillin (units).....	2000-10,000
Sodium heparin.....	0.002

\* This solution is a slight modification of "A" solution that was used experimentally and recommended by Abbott and Shea.<sup>30</sup>

† 50 to 100 gm. of dextrose per liter of solution was used in our case; however, 100 gm. per liter produced excessive dehydration and shock. By using 50 gm. per liter, a very good balance between peritoneal intake and output was obtained.

The solution employed was modified from "Solution A" of Abbott and Shea.<sup>70</sup> Their solution was made hypertonic by the addition of 10 to 20 grams of dextrose per liter. Through error we employed 10 per cent dextrose, or 100 grams per liter, in the initial stage of irrigation. Table 1 shows the composition of our solution after correcting this error.



FIG. 2. Photograph of patient during peritoneal irrigation.

During the first 36 hours of this period the patient received intraperitoneally 20,000 c.c. of solution, while the return from the peritoneal cavity was 25,330 c.c. At this time she developed shock as represented by a precipitous fall in blood pressure.

rapid pulse rate, disorientation, increase in total serum protein, and a rise in the hemoglobin to 15 gm. This complication was overcome by the administration of large amounts of parenteral fluids including whole blood and plasma and by reducing the dextrose content of the peritoneal irrigation solution to 50 gm. dextrose per liter. After this step was taken no further difficulty was encountered which could be attributed to hypertonicity of the irrigation solution.

A very good balance between peritoneal inflow and outflow was obtained and during the six-day period of peritoneal irrigation the total peritoneal inflow was 69,000 c.c. with 72,800 c.c. outflow. 14,640 c.c. of plasma, whole blood, and crystalloid solutions were administered parenterally during that time and 3000 c.c. of fluids were retained by mouth.

Thirty-six hours after the institution of peritoneal lavage the blood nonprotein nitrogen had fallen to 144 mg. per cent and she began retaining fluids by mouth.

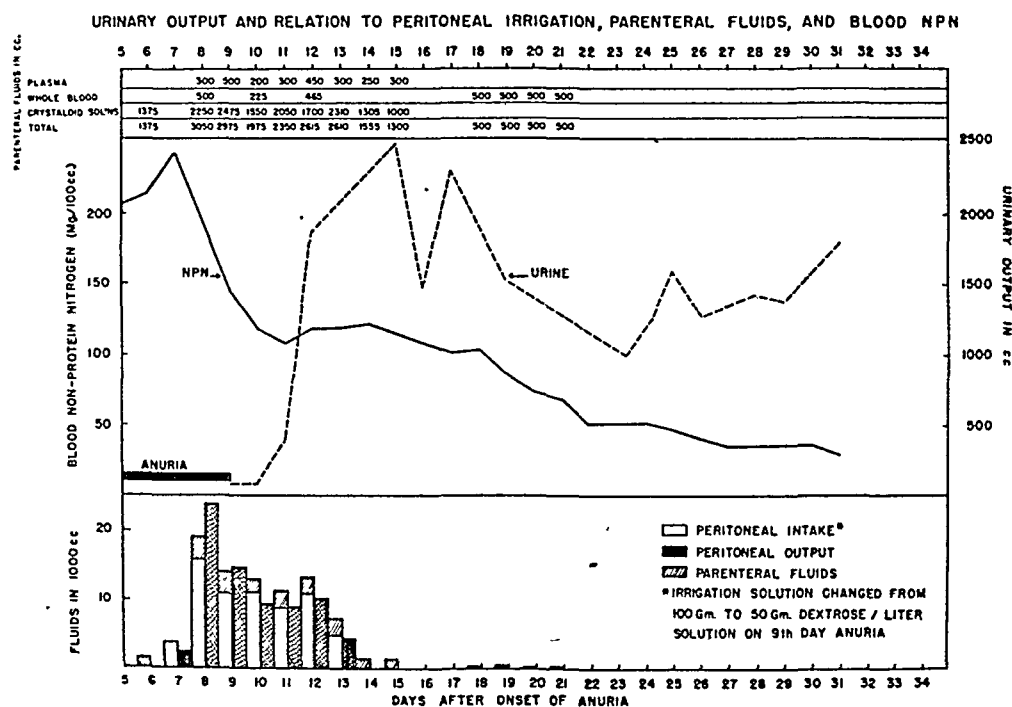


CHART 1.

On the ninth day, three days after the irrigation was started, she voided 90 c.c. of cloudy urine. Her subsequent urinary output was 90 c.c. on the tenth day, 500 c.c. on the eleventh day, and 1850 c.c. on the twelfth day. Thereafter output increased daily as did her fluid intake by mouth. The blood nonprotein nitrogen rapidly decreased as can be seen in chart 1.

On the eleventh day the patient developed a temperature elevation to 101.2° and the following day to 101.4°. She vomited on several occasions and complained of generalized abdominal pain. No peristalsis could be heard on examination of the abdomen, and it seemed apparent that she had peritonitis and paralytic ileus. Wangenstein's suction was started and she was given intramuscular streptomycin, 4 gm. daily in divided doses.

She had been on penicillin intramuscularly and peritoneally throughout the procedure with a blood level, before the development of peritonitis, of .435 unit per c.c.

Prior daily cultures of the peritoneal fluid had revealed no organisms but the culture taken just before the administration of streptomycin showed a strain of *B. pyocyaneus* which was subsequently found to be sensitive to 8 units of streptomycin per c.c. On the above dosage the blood streptomycin level reached 32 units per c.c. In spite of general improvement, the odor of pyocyaneus could be detected throughout the patient's room on the second day of peritonitis and her abdominal dressings were stained with a foul smelling greenish material. She improved rapidly on streptomycin therapy and by the third day all signs of peritonitis had disappeared.

By the thirteenth day she was voiding approximately 1500 c.c. every 24 hours, blood non-protein nitrogen was 118 mg. per cent and other blood chemistry values were approaching normal limits. It was decided that the patient's renal function was sufficient to maintain life and would probably continue to improve so peritoneal irrigation was discontinued.

As the patient recovered from paralytic ileus, she began having frequent loose, foul smelling, bloody stools. This continued from the sixteenth to the twenty-second

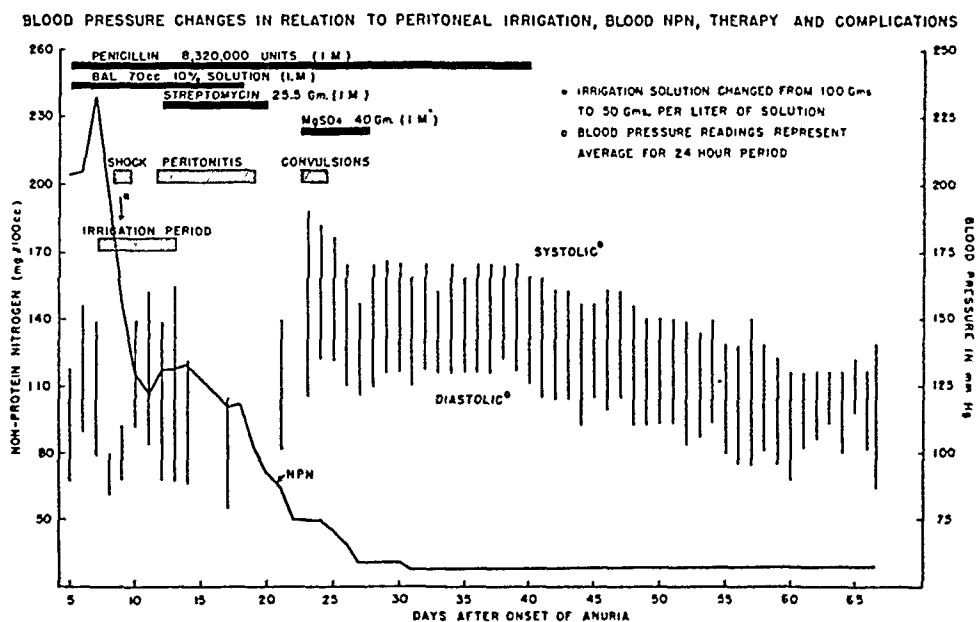


CHART 2.

day and then ceased rather abruptly. Sigmoidoscopy was performed on the twenty-second day but no areas of ulceration or bleeding could be visualized.

Stool specimens collected from the eleventh through the seventeenth day (almost entirely from the sixteenth and seventeenth days of her illness) contained 20 to 25 mg. of metallic mercury.

In general she improved until the twenty-third day when she complained of inability to see and within 10 minutes began to have an extremely severe generalized convulsion. At this time her blood pressure, which previously ranged from 105/60 to 155/40, was found to be 194/120. She was started on treatment with intramuscular magnesium sulfate which temporarily relieved the arterial spasm and produced a definite decrease in her blood pressure. On the following day she was again rational but complained intermittently of inability to see. She continued to receive magnesium sulfate and, over a period of five days, received a total of 40 gm. At this time her blood pressure was still approximately 170/125. A cold pressor test and deep sedation

with intravenous sodium amytal produced no appreciable fluctuation of blood pressure. Her blood pressure did, however, fall slowly and progressively throughout the remainder of her hospitalization and was 130 mm. Hg systolic and 100 mm. diastolic when she was discharged on the sixty-fifth day. One month after discharge from the hospital the blood pressure was 117/72. The blood pressure changes during hospitalization may be seen in chart 2.

In the period of convalescence she developed a mild hypochromic anemia which responded well to iron therapy.

On the thirty-first day her blood nonprotein nitrogen was 28 mg. per cent and all other plasma chemistry values were within normal limits. Her urine was clear and straw-colored with a pH of 6.0, albumin negative, and sugar negative. Microscopic examination of an uncentrifuged specimen revealed 1 white blood cell per high power field and no other cells, casts, or crystals were noted. Specific gravity of urine fluctuated between 1.010 and 1.022. Intravenous phenolsulfonphthalein test showed 5 per cent dye recovered in 15 minutes, 20 per cent in the 30 minute specimen, 20 per cent in the one hour specimen and 15 per cent in the two hour specimen, or a total of 60 per cent in two hours. Intravenous pyelography showed the kidneys to be of average size, shape and position with good concentration of the dye bilaterally and with fairly complete filling of the calyces, pelves and upper ureters bilaterally. There was some blunting and dilatation of the calyces and on the upright film there was delayed drainage bilaterally. Repeated urine cultures yielded no growth.

Electrocardiography showed no abnormality.

During her illness the patient did not have one of her regular menses and developed a rather heavy growth of hair over her entire body. Later her menses recurred and the hirsutism decreased progressively.

At the time of discharge on the sixty-fifth day her appetite was good, she had no complaints, and was gaining weight consistently. The hospital course, complications, and therapy are shown in charts 1 and 2.

A tabulation of the changes in plasma constituents and fluid exchange occurring during hospitalization is shown in appendix table 1.

The patient returned to the outpatient clinic 30 days after discharge in apparent excellent health and having gained 20 lbs. in weight. The blood non-protein nitrogen was 28 mg. per cent, a random urine specific gravity was 1.022 and her blood pressure was 117/72.

## DISCUSSION

A number of errors were made during this experience with peritoneal irrigation, and we believe that many improvements in the technic can be outlined.

An abundance of trained personnel is necessary in order to manage this procedure properly. Our patient required the constant attendance of at least one nurse and an immediately available physician. On many occasions several members of both the house staff and nursing staff were occupied with this one patient.

Extreme care should be taken in the preparation of the patient and the selection of the equipment prior to the institution of peritoneal lavage. A completely aseptic technic should be observed at all times in manipulation of the tubing, bandages, changing of the reservoir, etc. Large reservoirs such as 15 liter flasks would lessen dangers of contamination by reducing the number of changes involved. As suggested by Fine and his group<sup>32</sup> a sump

TABLE II  
Changes in Plasma Constituents and Fluid Balance

Days after Onset of Anuria	Blood N.P.N. mg./100 c.c.	Plasma CO <sub>2</sub> Vol. %	Plasma Protein gm./100 c.c.	Plasma Chlorides m.eq./liter	Plasma Phosphorus mg./100 c.c.	Blood Sugar mg./100 c.c.	Hgb. gm.	NaHCO <sub>3</sub> I.V. in gm.	Fluid Intake P.O. in c.c.†	Urine Output in c.c.	Irrigation Fluid		Parenteral Fluids in c.c.			Total
											Intake in c.c.	Output in c.c.	Plasma	Whole Blood	Crystalloid Solutions	
5	203	32.4		72.9	14.8		10.5		-340	0					1375	1375
6	212			69.9	11				-580	0						
7	240	34.4	5.43	71.7	10.7	1180	12		460	0						
8			6.97				14.5		1040	0	4000 <sup>1</sup>	2235				
9	144	31.2	6.02	80.4			15	12.5	963	0	16000 <sup>1</sup>	23095	300	500	2250	3050
10	116	36.2	5.30	82.5	4.7	395	14		11000 <sup>†</sup>	90	11000	14200	500		2475	2975
11	106	33.4	4.97	87.6	5.6	139	11	20.0	-350	75	9000	9485	200	225	1550	1975
12	118	53.2	4.5	86.4	7.0	118	11	14	75	380	9000	9250	300		2050	2350
13	118	89.9	4.98	87.3	7.4	166	11	4	-175	1841	11000	10120	450	465	1700	2615
14	120	77.7	4.93	95.1	7.4	110			425	595*	5000	4420	300		2310	2610
15									1600	435*			250		1305	1555
16	106	60.6	5.36	107.7	5.6	110			2325	2470			300		1000	1300
17	100	49.4	4.76	110.7	4	102			2350	1450						
18	102	52.2	4.82	102.4	3.5	98	8		3825	2265						
19	84	49.5	5.24	112.5			6		2350	1910				500		500
20	72	50.4	5.27	111.3	2.6	90	8		1160	1560				500		500
21	67	52.2	5.96	111.3	3.6	93	10.5		1170	760*				500		500
22	49	50.4	5.68	108.3	3.3	84	12		1950	700*				500		500
23							12		1130	380*						
24	50	50.4	6.37	109.3	3.3	84			700	955						
25	45								1600	1225						
26	39								1550	1570						
27	31						11.5		1830	1240						
28									1750	850*						
29									2000	1400						
30	33		5.52						1150	1350						
31	28								2225	2225						
Total									1510	1510	68000	72805	2600	2190	14640	20430

<sup>1</sup> Irrigation fluid contained 100 gm. dextrose per liter solution.<sup>†</sup> Irrigation fluid through remainder of irrigation period contained 50 gm. dextrose per liter solution.

Incontinent or urine mixed with water stools.

<sup>†</sup> A deficit of fluids in this column represents excessive emesis.



drain \* should be used as an outflow tube. They used an elaborate set-up for keeping the irrigation solution warmed to a temperature of 40 to 45° C. During the greater part of the irrigation period, we allowed the fluid to flow into the peritoneal cavity at room temperature and the patient experienced no discomfort. We are of the opinion that warming the solution is not necessary.

We believe that the irrigation solution should be made hypertonic by the addition of 30 to 50 mg. dextrose per liter in order to facilitate the abstraction of the excess interstitial fluid and solutes, and to reduce the risk of developing pulmonary edema. This increased glucose will also contribute to the satisfaction of the caloric requirements of these patients (several hundred calories from the glucose can be furnished the patient each day). This, of course, should be subject to individual variations and the dextrose content of the irrigating solution should be adjustable. The aim should be toward a balance between the peritoneal inflow and outflow and this is, of course, dependent on the tonicity of the irrigating solution. A step in the direction we have indicated was made by Fine and his group<sup>32</sup> suggesting an increase from 0.15 per cent glucose to 2 per cent.

Facilities should be available for frequent determinations of blood non-protein nitrogen, plasma CO<sub>2</sub>, plasma protein, plasma chloride, hemoglobin values, and at times other special determinations. We found that, in the process of peritoneal irrigation, fluid and electrolyte shifts occurred so suddenly that physical examination alone was apt to be misleading.

Sodium sulfadiazine probably should be added to the irrigation solution, except where the treatment is used for anuria due to sulfonamide intoxication. During the last 24 hours of peritoneal irrigation our solution contained 50 mg. per cent of sodium sulfadiazine and a blood level of 5.9 mg. per cent was obtained. A sulfadiazine level of 10 to 20 mg. per cent in irrigation solution would be more effective than penicillin as a prophylaxis against the gram-negative bacilli, the most likely contaminants, since these are in general more sensitive to sulfadiazine. The inclusion of both sulfadiazine and penicillin in the fluid would be ideal. We believe that streptomycin should be kept in reserve for vigorous treatment if peritonitis develops in spite of the above precautions. The use of low levels of this antibiotic in the irrigation solution prophylactically would be liable to lead to the development of streptomycin resistant organisms.

The fact that our patient had amenorrhea and developed temporary generalized hirsutism following peritoneal irrigation makes it seem quite possible that, with the dialysis of solutes there was also a transferral of hormones from the plasma and interstitial fluids to the irrigating solution. Abbott and Shea<sup>30</sup> postulated this possibility. As was noted above, our patient is now

\* These drains are usually constructed so that there is an open space between the perforated casing and the suction tip. This opening increases the chances of contamination because fluid can escape into the dressings unless continuous suction is applied. By using a screw cap to eliminate this space, a closed system is established and peritoneal drainage occurs as intra-abdominal pressure is increased.

having regular normal menses and, when last seen, the hirsutism was rapidly disappearing. This question should be investigated further.

The development of hypertension in our patient was to us a very interesting phenomenon. To our knowledge, this complication has not been encountered previously in experimental or clinical mercury poisoning. Although BAL may produce hypertension, this occurs within 30 minutes following an injection and rapidly disappears.<sup>33, 31</sup> The marked hypertension in our patient developed four days after BAL was discontinued. It, therefore, seems probable that this complication occurred as a result of the severe renal damage and that it has not been observed previously in mercury poisoning because patients with such a degree of renal damage have not lived long enough for this complication to develop. Edwards<sup>35</sup> made a very interesting observation in connection with this speculation. In studying the effects on the tubules of lethal amounts of mercury injected intravenously into animals, he found that the kidney of two of his rabbits, in addition to tubular damage, showed marked glomerular damage with enlarged capsular spaces and an occlusive constriction of the neck of the tubules. These two particular rabbits had lived for three to four months after mercury poisoning. The other animals, including rabbits, guinea pigs and rats, lived only 1 to 15 days and did not show such occlusions. He pointed out that "it is possible that a like occlusion would have occurred in the kidneys of most of these animals if they had lived long enough after the bichloride of mercury was injected."

It is difficult to evaluate the importance of BAL therapy in this patient. The fact that mercury was recovered from the colon contents in appreciable amounts on the sixteenth and seventeenth days makes it seem likely that BAL was still being effective in mobilizing mercury and in preventing further injury by mercury being excreted.

### A SUGGESTED THERAPEUTIC PLAN

In view of recent developments, it seems likely that the mortality in acute mercury poisoning can be greatly reduced.

For the treatment of acute mercury poisoning the following plan would seem desirable.

1. BAL should be administered immediately, preferably in the emergency room or home, to patients who are suspected of having ingested bichloride of mercury. The initial injection should be 3.5 to 4.5 mg.\* per kilo of body weight followed in two hours by 2 to 3 mg. per kilo and at intervals of six hours by four additional doses of 2 to 3 mg. per kilo. Thereafter one should administer 2 to 3 mg. per kilo twice daily until all evidence of poisoning has disappeared.

2. Gastric lavage should be carried out immediately and thoroughly. Four per cent sodium bicarbonate solution, always easily available, is prob-

\* The large per kilogram dose should be used in small individuals and young children may require even greater doses.

ably as effective as any other solution in the removal of excess mercury. Colonic flushings should be done approximately twice daily.

3. Every effort should be made in early severe cases to prevent shock. This requires the administration of whole blood, plasma, and crystalloid solutions.

4. Every effort should be made to maintain the fluid and electrolyte balance and to prevent dehydration or edema. Frequent determinations of blood nonprotein nitrogen, plasma CO<sub>2</sub> combining power, plasma proteins, plasma chloride, and hemoglobin are necessary in adjusting the regime.

5. In patients who are anuric, peritoneal irrigation may effectively remove metabolic wastes until renal function returns. The time at which this procedure should be started depends entirely on the condition of the patient and each case should be judged separately. It is never indicated unless the prognosis is otherwise considered to be extremely grave.†

### SUMMARY

1. The evolution of the treatment for acute mercury poisoning is discussed.

2. A patient with severe mercury poisoning treated with BAL and whose prolonged anuria was combated successfully by peritoneal irrigation is reported. These therapeutic measures are discussed in detail.

3. An outline for the treatment of acute mercury poisoning is proposed.

### BIBLIOGRAPHY

1. BERGER, S. S., APPLEBAUM, H. S., and YOUNG, A. M.: Immediate cecostomy and constant lavage in mercuric chloride poisoning, *Jr. Am. Med. Assoc.*, 1932, xcvi, 700.
2. GOLDBLATT, S.: Acute mercurial intoxication; report of 38 cases, *Am. Jr. Med. Sci.*, 1928, clxxvi, 645.
3. WEISS, H. B.: Mercuric chloride poisoning, *Arch. Int. Med.*, 1924, xxxiii, 224.
4. PETERS, JOHN P., EISENMAN, A. J., and KYDD, D. M.: Mercury poisoning, *Am. Jr. Med. Sci.*, 1933, clxxxv, 149.
5. HULL, EDGAR, and MONTE, L. A.: Acute mercury poisoning, *New Orleans Med. and Surg. Jr.*, 1935, lxxxviii, 455.
6. LONGCOPE, W. T., LUETSCHER, J. A., JR.: Clinical uses of 2, 3-dimercaptopropanol (BAL). XI. The treatment of acute mercury poisoning by BAL, *Jr. Clin. Invest.*, 1946, xxv, 9.
7. ROSENBLOOM, J.: A note on the distribution of mercury in the body in a case of acute bichloride of mercury poisoning, *Jr. Biol. Chem.*, 1915, xx, 123.
8. HAYMAN, J. M., JR., and PRIESTLEY, J. T.: Importance of diuresis in treatment of certain cases of mercuric chlorid poisoning, *Am. Jr. Med. Sci.*, 1928, clxxvi, 510.
9. LAMBERT, S. W., and PATTERSON, H. S.: Poisoning by mercuric chlorid and its treatment, *Arch. Int. Med.*, 1915, xvi, 865.
10. WEISS, H. B.: Methods of treatment of mercuric chloride poisoning, *Jr. Am. Med. Assoc.*, 1917, lxviii, 1618.
11. SUNDERMAN, F. W., AUSTIN, J. H., and CAMACK, J. G.: Studies of serum electrolytes. III. In infections, nephritis, and other pathological conditions, *Jr. Clin. Invest.*, 1928, vi, 37.

† Peritoneal irrigation is also indicated in the treatment of other acute reversible anuric states.

12. TALBOTT, J. H., COOMBS, F. S., and CONSOLAZIO, W. V.: Electrolyte balance during recovery from mercury bichloride poisoning, *Arch. Int. Med.*, 1937, lx, 301.
13. ROSENTHAL, S. M.: An antidote for acute mercury poisoning, *Jr. Am. Med. Assoc.*, 1934, cii, 1273.
14. MONTE, L. A., and HULL, E.: Mercury bichloride poisoning treated with sodium formaldehyde sulfoxylate, *Jr. Am. Med. Assoc.*, 1940, cxiv, 1433.
15. MUIR, K. B., STENHOUSE, E., and BECKER, S. W.: Action of sulphur-containing compounds in arsenic and mercury poisoning, *Arch. Dermat. and Syph.*, 1940, xli, 308.
16. MINTZ, E. R.: Some remarks on treatment of bichloride of mercury poisoning with presentation of 21 cases, *New England Jr. Med.*, 1933, ccviii, 1189.
17. ANDERSON, J. H.: Successful treatment of a bichloride of mercury case by hydraulic irrigation through cecostomy operation, *Surg., Gynec. and Obst.*, 1915, xx, 350.
18. JOHNSTONE, B. I.: Acute mercury poisoning; report of 21 cases with suggestions for treatment, *Canad. Med. Assoc. Jr.*, 1931, xxiv, 500.
19. HASHINGER, E. H., and SIMON, J. F.: A case of mercuric chlorid poisoning treated by exsanguination-transfusion, *Jr. Lab. and Clin. Med.*, 1934, xx, 231.
20. PETERS, R. A., STOCKEN, L. A., and THOMPSON, R. H.: British Anti-Lewisite (BAL), *Nature*, 1945, clvi, 616.
21. WATERS, L. L., and STOCK, C.: BAL (British Anti-Lewisite), *Science*, 1945, cii, 601.
22. GINZLER, A. M.: The effect of BAL therapy on the renal lesion in mercury poisoning, *Federation Proc.*, 1946, v, No. 1, Part 2.
23. GILMAN, A., ALLEN, R. P., PHILIPS, F. S., and ST. JOHN, E.: The treatment of acute systemic mercury poisoning in experimental animals with BAL thiosorbitol and BAL glucoside, *Jr. Clin. Invest.*, 1946, xxv, 549.
24. PUTNAM, T. J.: The living peritoneum as a dialyzing membrane, *Am. Jr. Physiol.*, 1923, xliii, 548.
25. BLISS, S., KASTLER, A. O., and MADLER, S. B.: Peritoneal lavage. Effective elimination of nitrogenous wastes in the absence of kidney function, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 1078.
26. HAAM, E. V., and FINE, A.: Effect of peritoneal lavage in acute uremia, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxx, 396.
27. RHOADS, J. E.: Peritoneal lavage in the treatment of renal insufficiency, *Am. Jr. Med. Sci.*, 1938, cxcvi, 642.
28. WEAR, J. B., SISK, I. R., and TRINKLE, A. J.: Peritoneal lavage in the treatment of uremia, *Jr. Urol.*, 1938, xxxix, 53.
29. BALAZS, J., and ROSENAK, S.: Zur Behandlung der Sublimatanurie durch peritoneale Dialyse, *Wien. klin. Wchnschr.*, 1934, xlvii, 851.
30. ABBOTT, W. E., and SHEA, P.: The treatment of temporary renal insufficiency (uremia) by peritoneal lavage, *Am. Jr. Med. Sci.*, 1946, ccxi, 312.
31. SELIGMAN, A. M., FRANK, H. A., and FINE, J.: Treatment of experimental uremia by means of peritoneal irrigation, *Jr. Clin. Invest.*, 1946, xxv, 211.
32. FINE, J., FRANK, H. A., and SELIGMAN, A. M.: The treatment of acute renal failure by peritoneal irrigation, *Ann. Surg.*, 1946, cxxiv, 857.
33. SULZBERGER, M. B., RUDOLF, L. B., and ABRAM, K.: Clinical uses of 2, 3-dimercaptopropanol (BAL). III. Studies on the toxicity of BAL on percutaneous and parenteral administration, *Jr. Clin. Invest.*, 1946, xxv, 474.
34. MODELL, W., GOLD, H., and CATTELL, MCK.: Pharmacologic observations on BAL by intramuscular injection in man, *Jr. Clin. Invest.*, 1946, xxv, 480.
35. EDWARDS, J. G.: Renal tubule as affected by mercury, *Am. Jr. Path.*, 1942, xviii, 1011.

# ELECTROCARDIOGRAPHIC CHANGES IN DIPHTHERIA \*

By SAMUEL S. ALTSHULER,<sup>†</sup> Major, F.A.C.P., KELSE M. HOFFMAN,<sup>‡</sup>  
Major, F.A.C.P., and PATRICK J. FITZGERALD,<sup>§</sup>  
Captain, M.C., A. U. S.

THE free use of the electrocardiogram in military hospitals and an epidemic of diphtheria among unimmunized troops presented an opportunity for a reevaluation of the non-specific electrocardiographic changes occurring in diphtheritic infections.

During combat, diphtheria was not a serious problem among the United States Forces, European Theater. Following the surrender of Germany in May 1945 and the closer concomitant contact of troops with the indigenous population, the incidence of the disease increased rapidly and reached epidemic proportions in the first five months of 1946. The incidence of diphtheria among troops of the United States Forces, European Theater and in the civilian populations of Germany and France is shown in figure 1.<sup>1</sup>

In 1944 there were only 248 cases of diphtheria among the United States Army troops in the European Theater. During 1945 there were 2153 cases and in 1946 there were 1604 reported cases. However, the case rate reached a peak in 1946 since the Theater troop strength was much smaller.<sup>1</sup>

All reported cases were confirmed bacteriologically. In the last six months of 1946, of 432 strains typed at the Theater medical laboratory, 55.3 per cent were of the mitis strain, 42.6 per cent of the gravis strain and 2.1 per cent of the intermedius strain.<sup>1</sup> Of the gravis strains, 97 per cent proved virulent as did 86 per cent of the mitis strains and 68 per cent of the intermedius strains.<sup>1</sup>

In a 1,000 bed general hospital in the American Occupied Zone of Germany, 600 patients with diphtheria were seen in the 15 month period from September 1945 to December 1946. This number included 26 cases of cutaneous diphtheria. The patients were male American soldiers with the exception of 37 drawn variously from female American military personnel, allied military personnel and civilian employees of the War Department. The youngest patient was 18 years old, the oldest 43, and the average age was 23.4 years.

The portable "Cardiette" was the only instrument employed. All tracings were standardized with a deflection of 1 cm. representing 1 millivolt of potential. A tracing consisted of the three limb leads and the precordial Lead CF<sub>6</sub>. Leads from other precordial points were not taken routinely.

\* Received for publication September 12, 1947.

From the Medical Service, 97th General Hospital, APO 757, c/o PM, N. Y., N. Y.

<sup>†</sup> Chief of Medical Service.

<sup>‡</sup> Formerly Assistant Chief of Medical Service.

<sup>§</sup> Assistant Chief of Medical Service.

An electrocardiogram was recorded as soon as diphtheria was suspected clinically or when a positive culture was reported. Thereafter electrocardiograms were recorded at weekly intervals or more often when indicated. Patients were restricted to bed until two normal electrocardiograms had been recorded after which they were permitted ambulation if afebrile and asymp-

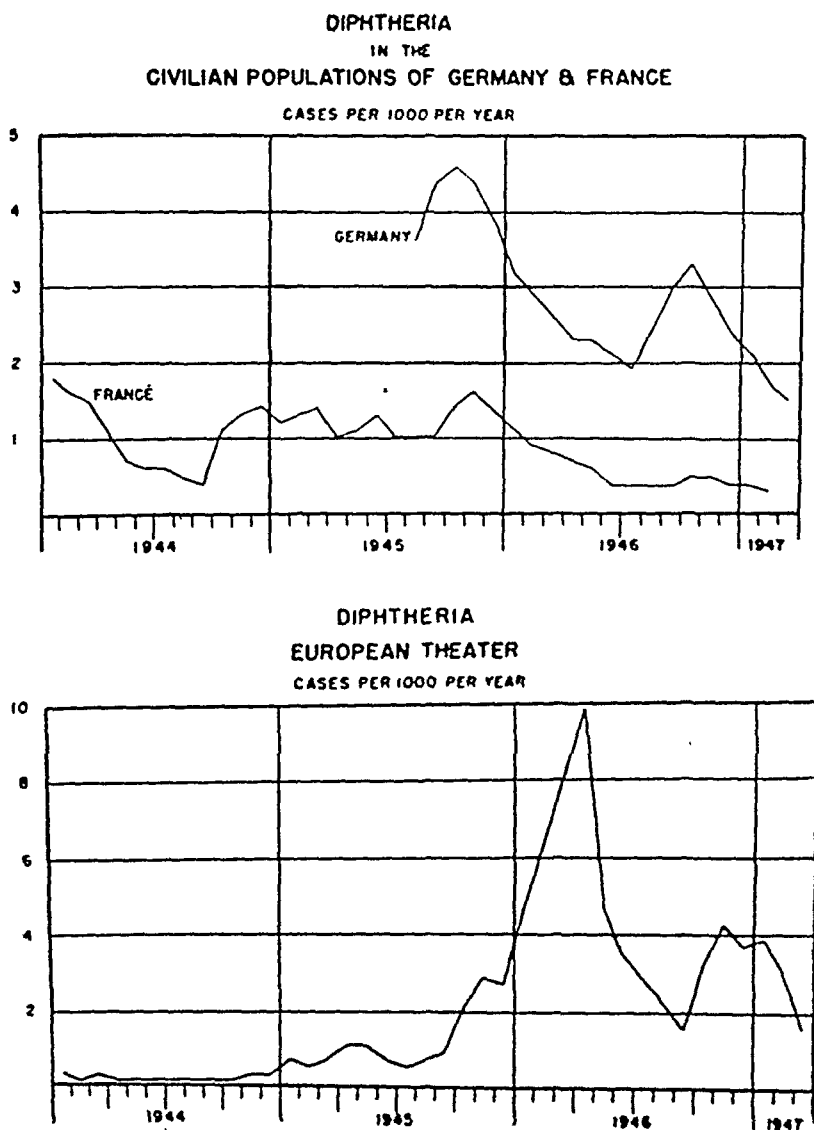


FIG. 1.

tomatic. An electrocardiogram was recorded the day before discharge. Patients were hospitalized for a minimum of five weeks. The criteria of cure were absence of symptoms and evidence of infection, three consecutive negative nose and throat (or cutaneous ulcer) cultures and an electrocardiogram within normal limits. American military personnel with severe or

prolonged electrocardiographic changes were invariably returned to the United States for convalescence. The period of observation for patients with electrocardiographic changes varied between eight and 23 weeks.

Of the 600 cases of diphtheria studied, 143 (23.9 per cent) presented electrocardiographic changes at some time during hospitalization. All electrocardiograms were read by one of two persons and independent interpretation of the same tracing revealed a high degree of correlation.

The electrocardiographic abnormalities noted are presented in table 1:

TABLE I  
ECG Abnormalities Noted in Routine Study of 600 Cases of Diphtheria

Abnormality	Number of Cases
A. Low or negative T in two or more leads	108
B. Depressed ST segments in two or more leads	10
C. Prolonged PR interval	11
D. Sinus bradycardia	8
E. Sinus tachycardia	5
F. Numerous ventricular premature beats	4
G. Decreased voltage of QRS in all leads	3
H. Prolonged QT	2
I. Bundle branch block (right)	2
J. Complete heart block	2
K. Wandering pacemaker	1
L. Temporary right axis shift	1
M. Temporary left axis shift	1

From table 1 it can be seen that the greatest number of abnormalities involved the T-waves and ST segments. Liberal standards of T-wave normality were adopted in view of the electrocardiographic findings in the study of a large number of presumably healthy aviation cadets.<sup>2</sup>

ST segment depressions were considered abnormal when they exceeded 1 mm. Abnormal ST segment depressions always occurred in two or more leads and corresponded to the ST segment depressions reported by Ball.<sup>3</sup> This change is illustrated in figures 2 and 3.

An isoelectric  $T_1$  was considered abnormal only if in the series  $T_1$  was at any time 2.0 mm. in height.  $T_2$  was judged to be abnormal if it was less than 2.0 mm. in height with concomitant upright  $T_1$  and isoelectric or upright  $T_3$ . In the presence of isoelectric  $T_1$  and isoelectric or negative  $T_3$ ,  $T_2$  was considered abnormal only if isoelectric or negative.  $T_3$  was regarded as normal unless it was initially upright and became diphasic or inverted.  $TCF_3$  was considered abnormal only if it became negative at some time during the period of observation. Twelve patients were noted to have persistent diphasic or inverted  $TCF_3$  with a normal ST segment as the only electrocardiographic finding; these were not considered significant. To avoid error, a tracing with T-wave abnormalities was considered significant only if T-wave changes were present in two or more leads. T-waves were not reported as abnormal because of the arbitrary standards of low voltage unless they had lost their characteristic configuration and had become broad and rounded. No cases with borderline tracings have been included; one

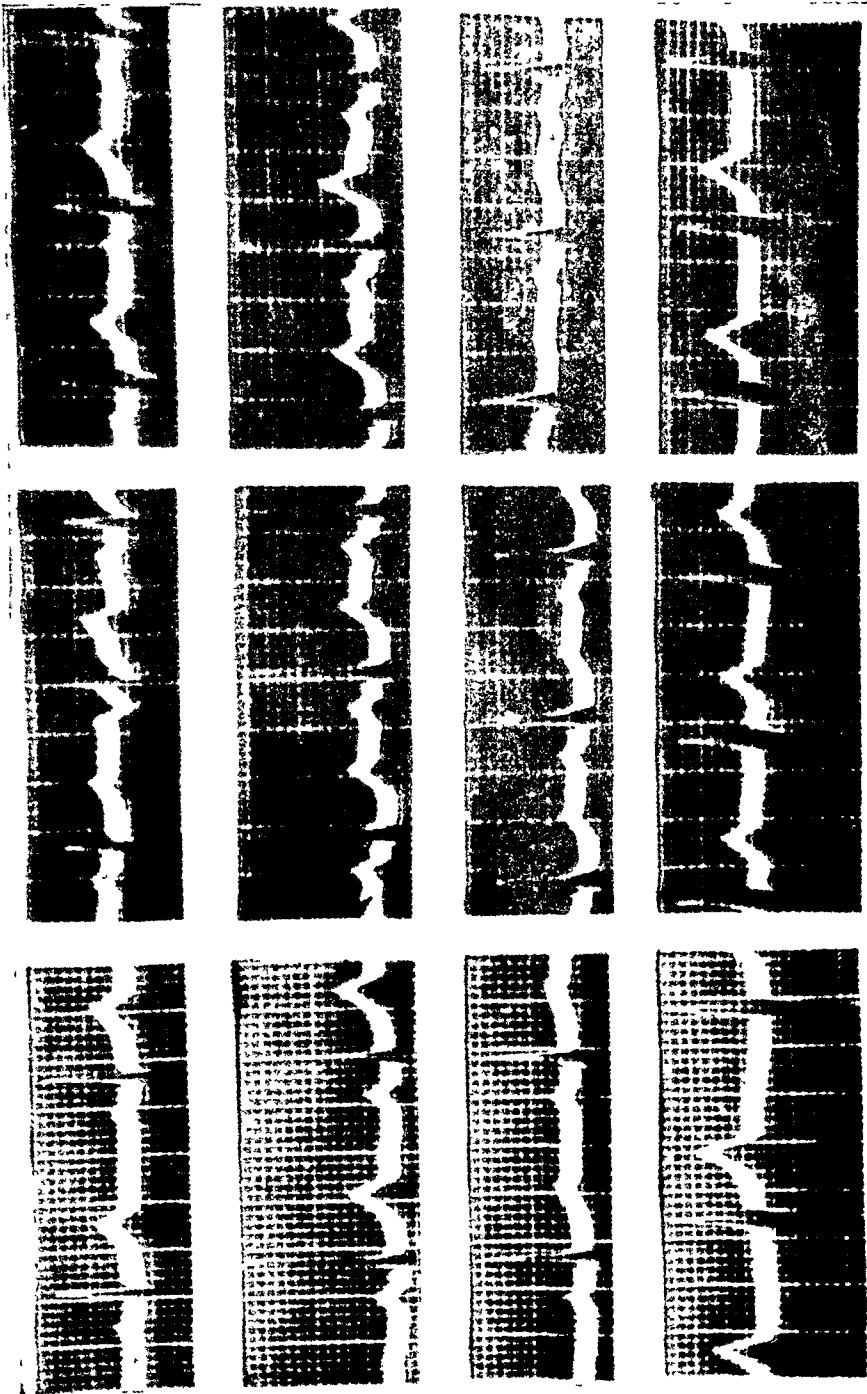


FIG. 2. Low origin and "saucer" of ST segment not yet present in the second week of illness, present in the third week and has disappeared in the fourth week.



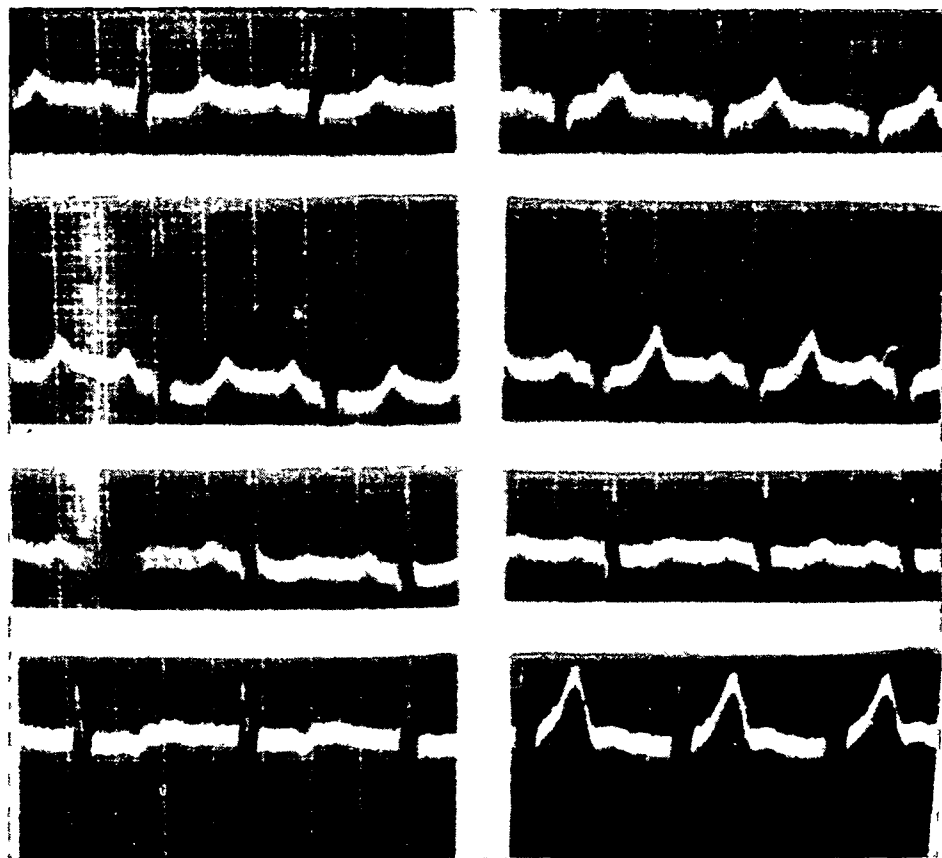


FIG. 3. Low origin and "saucerling" of ST segment in the second week; no longer present in the fourth week.

or more of these tracings was invariably preceded by indisputably normal or frankly abnormal tracings. Some of the T-wave changes noted are presented in figures 4 through 7.

Table 2 shows the combination of T-waves affected, the total number in each combination and the average duration in weeks.

TABLE II  
T-Wave Changes (Flattening to Complete Inversion)

T-Waves Involved	Number	Average Duration in Weeks
T <sub>1,2</sub>	2	3.0
T <sub>1,3</sub>	8	3.5
T <sub>1,4</sub>	5	4.5
T <sub>2,3</sub>	30	4.0
T <sub>2,4</sub>	4	2.5
T <sub>1,2,3</sub>	25	5.5
T <sub>1,3,4</sub>	6	4.5
T <sub>1,2,3,4</sub>	28	7.5
	<hr/> 108	<hr/> 4.3

T-wave abnormalities were noted most frequently in the limb leads and represented diffuse myocardial involvement. Abnormalities generally per-

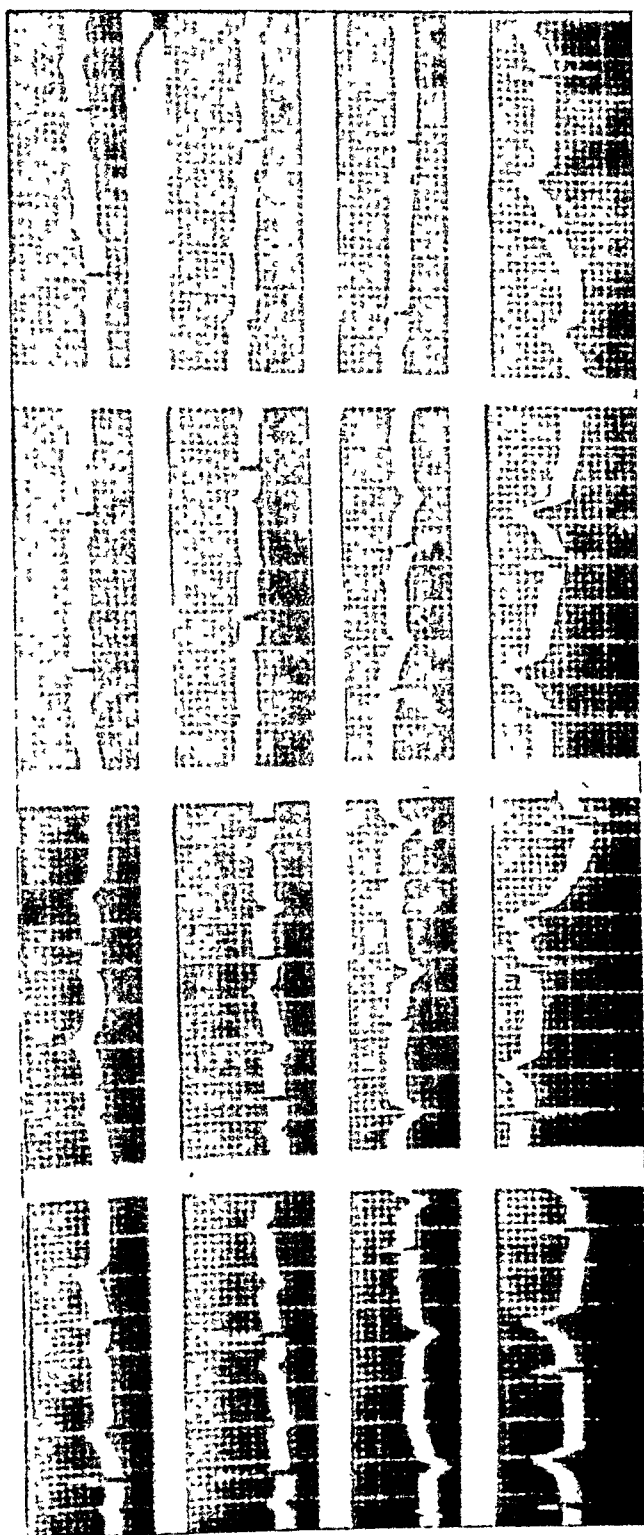


FIG. 4. Inversion of  $T_2$  and  $T_3$  in the second, third and fourth weeks of illness. T-waves in all leads are normal in the fifth week.

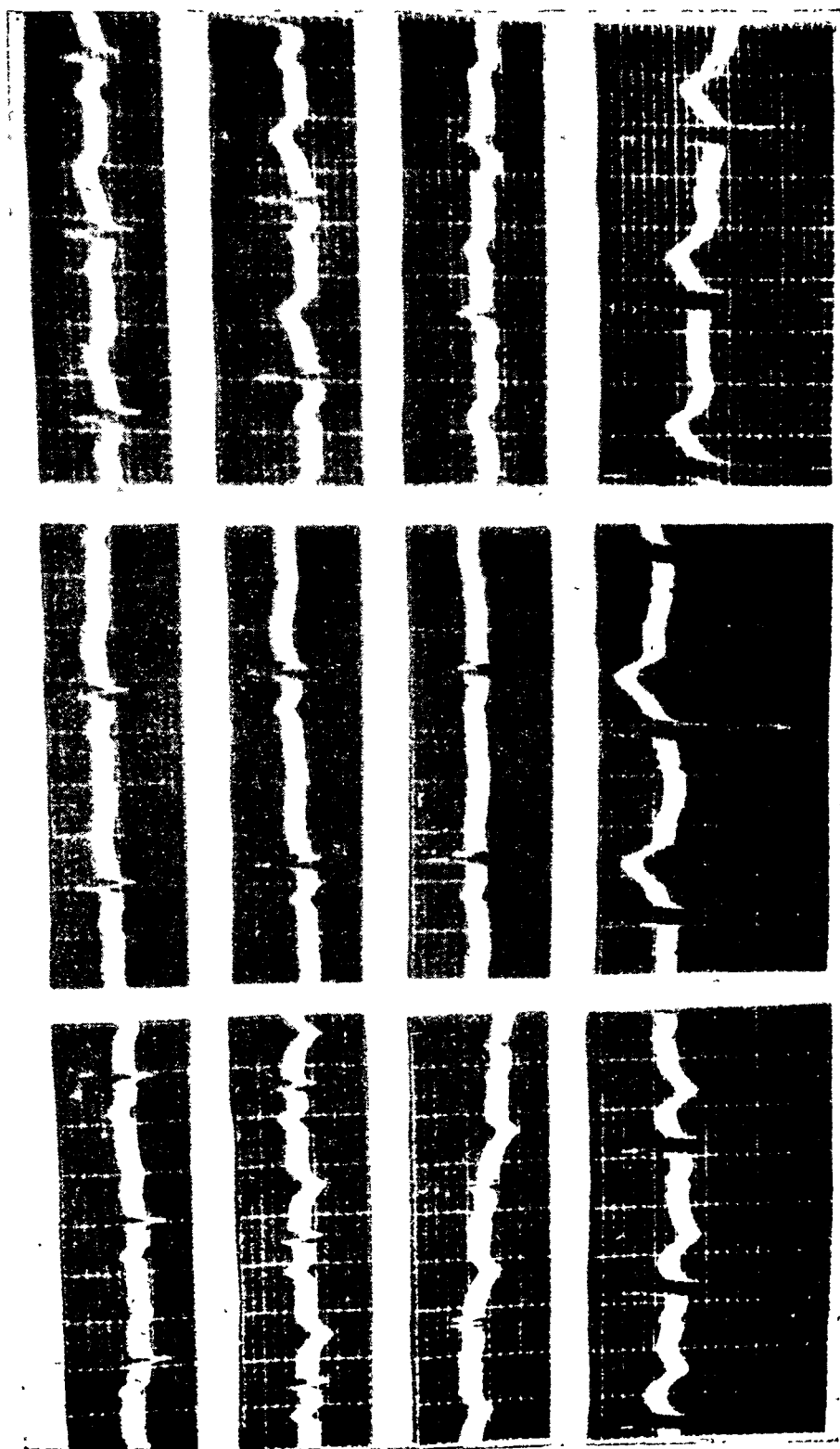


FIG. 5. Inverted T-wave in all leads and marked decrease in amplitude of QRS. Tracings shown are in the second, seventh and thirteenth weeks of illness.

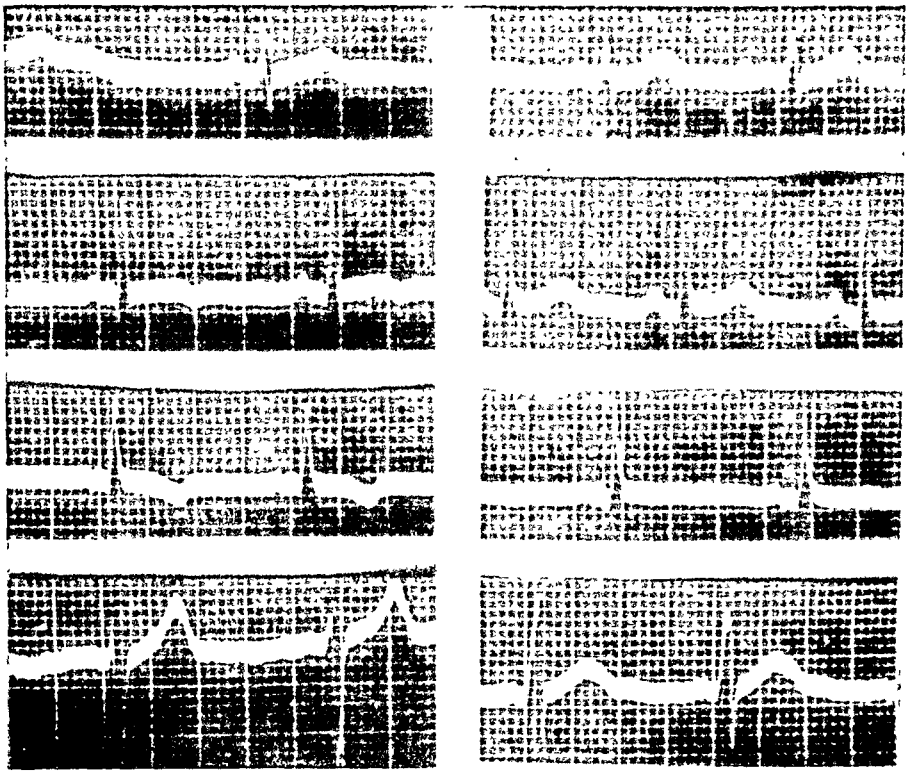


FIG. 6. Inversion of  $T_2$  and  $T_3$  occurring in the second week and returning to normal configuration in the fourth week.

sisted directly in proportion to the number of leads involved—this is well borne out by the 7.5 week average duration of abnormalities present in all four leads. T-wave abnormalities persisted for from two to longer than 23 weeks. Patients with persistent abnormalities in all leads usually had manifested clinically severe infections.

QRS complex changes were infrequent. Slight slurring and splintering were common but the only significant prolongation occurred in the two patients with right bundle branch block. Low voltage QRS in all leads occurred in three cases and accompanied low voltage T-waves.

Prolonged QT was observed twice and did not persist. One patient showing this change had a moderately severe pharyngeal diphtheria, no other electrocardiographic changes, but an acute anxiety reaction with hyperventilation.

Sinus bradycardia (rate less than 50 in the absence of heart block) was observed in eight patients who eventually had stable rates between 70 and 80. The slowest rate recorded was 42. Sinus tachycardia (rates of 130 or more and disproportionate to fever) occurred in five patients.

The upper limit of normal for the PR interval was considered to be 0.22 sec. and this was regarded as abnormal if the PR interval in any electrocardiogram of a series was less than 0.20 sec. (with rate considered). Pro-

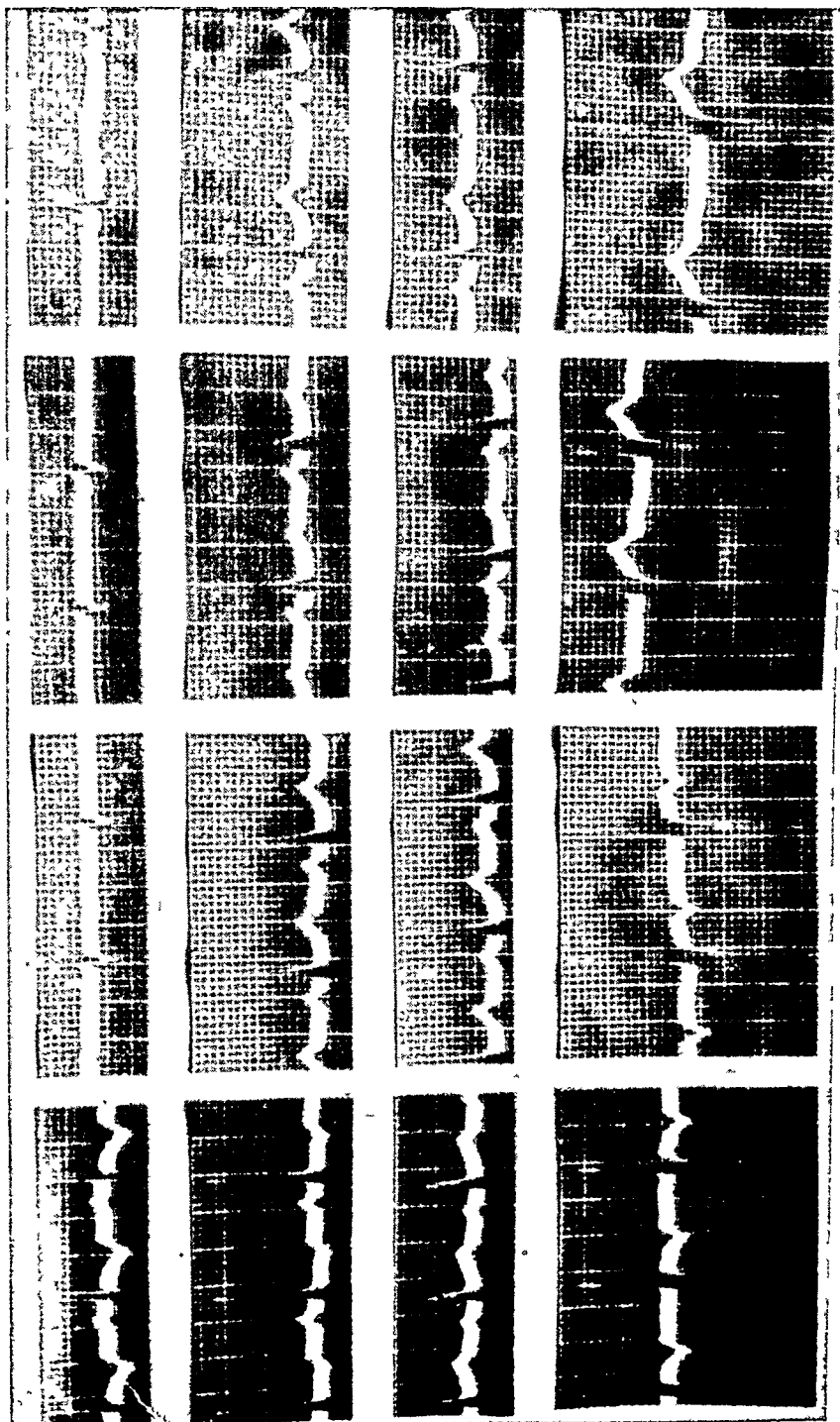


FIG. 7. T-wave changes in Leads I, II and IV and temporary right axis shift. Tracings shown are in the third, sixth, seventh and eleventh weeks of illness.

longation of the PR interval occurred in 11 patients (excluding two with complete A-V block). The commonly held opinion that prolongation of the PR interval is the most common abnormality in diphtheritic infections was not substantiated by this study.

The two patients with complete heart block had remarkably parallel courses. Each had a previous admission because of exudative tonsillitis, one with a small peritonsillar abscess. Beta hemolytic streptococcus was cultured from the throat of each and a gratifying response was obtained with sulfadiazine in one case and intramuscular penicillin in the other. They were both returned to duty within the week, completely asymptomatic. One patient was returned to the hospital after six days, the other after eight because of weakness and syncope. Upon admission, each was in cardiovascular collapse. Complete heart block was diagnosed clinically and substantiated by the electrocardiogram. *Corynebacterium diphtheriae* (*gravis*, virulent) was cultured from the pharynx of both patients. The electrocardiogram of one patient was normal after six weeks, that of the other after 10 weeks. Following subsidence of the complete block, the only abnormality was prolongation of the PR interval (maximum 0.44 sec.). Recovery was uneventful.

Right bundle branch block in two patients persisted for three and five days after which there was deep inversion of all T-waves. The electrocardiogram was not within normal limits after 18 weeks in one patient nor after 23 weeks in the other.

Of the 26 patients with cutaneous diphtheria, four had electrocardiographic abnormalities. One patient with a single 3 by 4 cm. ulcer on the lower leg had negative T-waves in all leads and eventually a severe generalized polyneuropathy.

Two deaths occurred in the series of 600 patients. Neither patient had bundle branch block at any time but both had negative T-waves in all leads. A photomicrograph of the myocardium is presented in figure 8.

Although realizing that statistical generalities may not be applied to individual cases, the study of these 600 patients permits the general observation that if a patient with diphtheria has not shown electrocardiographic changes by the end of the fourth week after the onset of his clinical infection, the possibilities of myocardial involvement from the disease are few. Only five patients presented their first electrocardiographic changes after the fourth week, three in the fifth week, one in the sixth week and one in the seventh week. One hundred twenty-one of the 600 patients were seen after the twentieth week following return to duty and all had normal electrocardiograms.

The electrocardiogram in diphtheria can occasionally be palindromic—abnormal at one time, normal several weeks later and abnormal again in a week or two. This phenomenon was observed four times in the series and in each instance the abnormality was negative T-waves. In one patient the

electrocardiogram alternated between normal and abnormal for eight weeks. No correlation could be established with persistence of the carrier state.

No correlation was possible between the severity of the infection and the severity of the electrocardiographic changes. The patients with the most marked and prolonged abnormalities usually had clinically severe infections

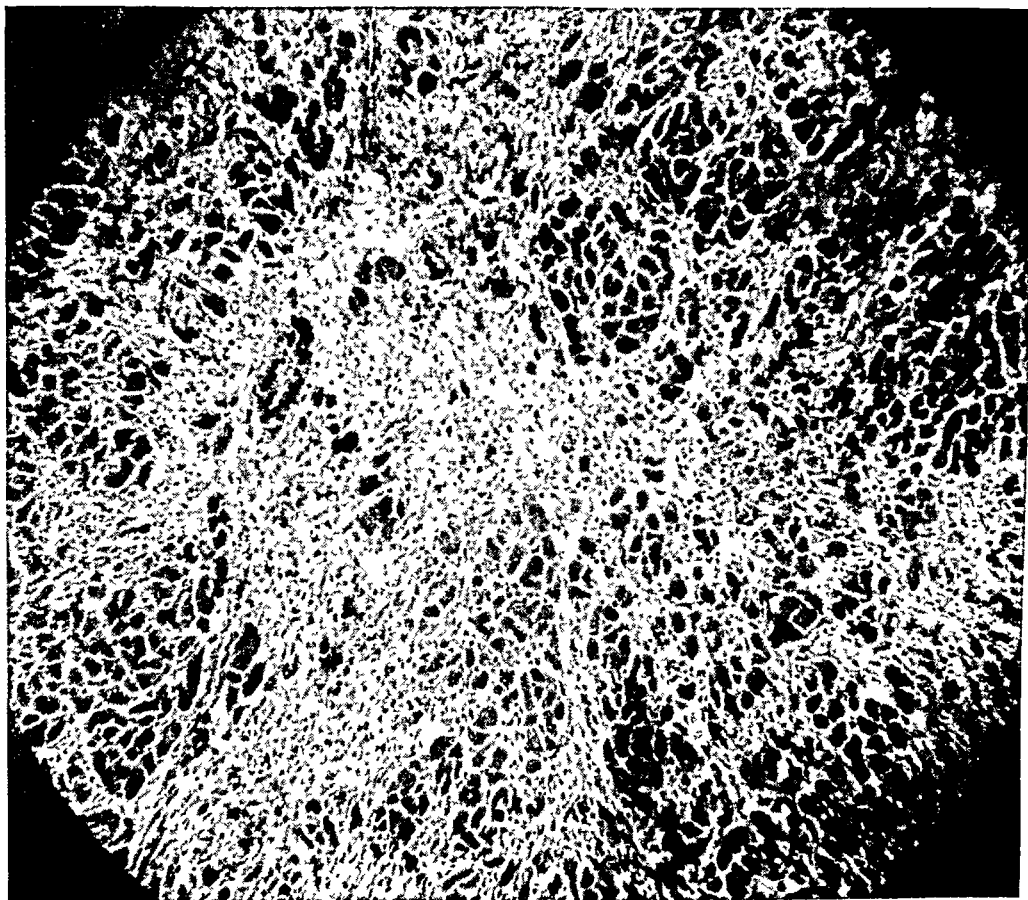


FIG. 8. Myocardial degeneration in a fatal case of diphtheria.

but some patients with mild infections who were asymptomatic after the first few days had marked and persistent electrocardiographic changes.

The presence of the most common abnormality, T-wave changes, could not be predicted by evaluation of the pulse, blood pressure determinations or auscultation of the heart.

#### SUMMARY

1. The electrocardiographic study of 600 consecutive cases of diphtheria is reported.
2. Significant electrocardiographic abnormalities were found in 143 cases (23.9 per cent).

3. The most frequent change was decreased voltage or negativity of the T-waves. The belief that PR prolongation is the most common finding in diphtheria was not substantiated.

4. Phasic alternation between normal and abnormal electrocardiograms in diphtheria was noted.

5. Severity of clinical infection and severity and duration of electrocardiographic changes in diphtheria cannot be correlated.

6. The electrocardiogram is essential in the evaluation of the physical state of patients with clinical diphtheria both in the acute and in the convalescent periods.

#### BIBLIOGRAPHY

1. SCHULZE, H. A.: Diphtheria in the United States Army in Europe, *Med. Bull. Office of the Chief Surgeon, European Command*, 1947, II, 2-26.
2. GRAYMEL, ASHTON, McFARLAND, R. A., GATTI, DONALD and WHEELER, FRED: Analysis of the electrocardiograms obtained from 1,000 young healthy subjects, *Am. Heart J.*, 1944, xix, 524.
3. BALL, DAVID: Diphtheritic myocarditis, with a report of two cases, *Am. Heart J.*, 1945, xxix, 704.



# BOECK'S SARCOID: OBSERVATIONS ON SEVEN PATIENTS, ONE AUTOPSY \*

By GAYLORD S. BATES, Comdr., MC, USNR, and JOHN M. WALSH,  
Lt. Comdr., MC, USNR, *Detroit, Michigan*

SEVEN patients with Boeck's sarcoid have come under our observation in a large Naval Hospital during the past 18 months. One died suddenly, permitting more complete study of the disease process. The circumstances surrounding the clinical course and final recognition of the disease in these patients have aroused our interest. We would like to transmit that interest to others, for we are certain that the disease is not uncommon and is, at present, resting uneasily under other diagnostic titles. Our postmortem observations in this one case of sudden death are of value and will be given in detail.

Boeck's sarcoid is not a rare disease. Many excellent clinical and pathological studies of it have been published. Its varied clinical features and its histological picture are well known, though its fundamental nature is not understood. It can usually be identified with certainty.

The infrequent recognition of this disease can be readily explained. Few physicians have made its acquaintance; nor is this remarkable. Only recently has it been realized that sarcoid may affect in its mild chronic relapsing course every organ in the body. At any one time only limited symptoms or signs may be present which go unrecognized as being a part of this disease picture, or more frequently, are mislabelled another disease. This reflects both the slow development of knowledge of Boeck's sarcoid, and its confusing clinical manifestations. An excellent historical summary and clinical review is to be found in the Frank Billings lecture of 1941 by Longcope.<sup>1</sup>

We shall present in tabular form the pertinent clinical facts of these seven patients. They illustrate how and under what circumstances the disease sarcoid may appear in clinical practice. Some observations are offered from this experience which may prove helpful in the recognition and the management of patients with this affliction.

In table 1, we note that these patients were young adults and that four of the seven were Negroes. This is in accord with common experience. Except in one instance, there had been intermittent symptoms for from four days to 10 months. The symptoms themselves showed no consistency, either alone or in combination, and served rather to suggest more common diseases as reference to the admitting diagnoses in table 3 makes evident. Similarly, the physical findings on admission to the sick list were no more than just consistent with the presenting symptoms, with one exception. The peculiar skin lesions seen in the first patient may have been distinctive

\* Received for publication May 21, 1946.

of Boeck's sarcoid. No skin biopsy was ever taken, and the significance of these lesions was not appreciated until after the patient returned to duty.

Table 2 presents the roentgenographic and the positive laboratory findings. Five of the patients had widened hilar shadows interpreted as evidence of enlarged lymph nodes in this location. In addition, signs of sarcoidosis in the lung parenchyma were observed in patient No. 5. At least, it seems fair so to interpret the development of peribronchial mottling in the chest. We know from histological evidence that this patient had almost universal involvement of voluntary muscle by sarcoidosis, that his disease was progressive during the six months under our observation, and that sarcoid

TABLE I

Case	Age	Sex	Race	Symptoms and Duration of Onset	Physical Findings on Admission
1	27	M	W	2 months—Weakness, pain in the head and neck, loss of weight, skin blemishes, swelling of glands in the groin.	Inguinal and axillary adenopathy. On arms and neck were raised blanched skin lesions 5–10 mm. in diameter.
2	22	M	W	10 months—Recurrent episodes of abdominal pain, nausea, vomiting, fever, and fleeting joint pains.	Generalized lymphadenopathy, pallor, fever, weight loss of 40 pounds, pulse rate of 100.
3	20	M	B	6 weeks—Swelling of the glands in the left side of the neck, slight fever.	Generalized lymphadenopathy, slight fever, swelling of the left arm.
4	26	M	W	4 months—Migrating joint pains following scarlet fever.	Fever, tender knee joints.
5	20	M	B	4 days—Pain in forearms, wrists, between the shoulders, bilateral parotid swelling.	Not remarkable except for fever, pulse rate 90 to 110.
6	27	M	B	0 days—No symptoms. Suspicious shadows on routine chest X-ray.	Not remarkable.
7	31	M	B	2 months—Anorexia, weakness, loss of weight, pain in the calves of the legs.	Generalized muscular atrophy. Pulse rate 90 to 100.

lesions are frequently found to be present in the lungs. Certain it is that enlarged mediastinal lymph nodes, as indicated by widened hilar shadows on the roentgenogram, are an important and early feature of this disease.

The laboratory procedures performed in each patient reflected in general the physician's desire to find a satisfactory diagnosis. It is not surprising that tuberculosis took first place in the differential diagnosis in view of the frequency of widened hilar shadows in the roentgenograms, low grade fever, weakness, and elevated sedimentation rate. In all patients acid fast bacilli were searched for in sputa and gastric washings without success. In one patient a tuberculin test was not done. In six it was negative, but in one of these, patient No. 5, it changed to positive on the fourth test, eight months

after the onset of sarcoidosis and while the disease was still active clinically. No other evidence of tuberculosis has yet made its appearance in this man.

The blood picture presented by these patients was not remarkable, even on repeated examination. In four, an elevated leukocyte count was present at some stage of the disease, though the differential was never abnormal. Eosinophilia appeared but once, in one patient, and was not confirmed by subsequent study. The serum protein in two patients was found to be elevated and in both the globulin fraction was above normal. Unfortunately, this feature was not looked for in the other five. The sedimentation rate was above normal in five patients upon their admission to this hospital and

TABLE II

Case	X-Ray Findings	Positive Laboratory Data
1	Chest—Repeated films showed hilar shadows, lung markings and parenchyma to be within normal limits.	SR up to 65. Lymph node biopsy—sarcoid.
2	Chest—Heart normal in size, lungs clear, and no evidence of mediastinal abnormality.	SR up to 52. Two lymph node biopsies—sarcoid.
3	Chest—Bilateral hilar adenopathy. Lung parenchyma clear.	One lymph node biopsy elsewhere—"possible tuberculosis." Similar biopsy here—sarcoid.
4	Widened hilar shadows with marked peribronchial infiltration in the right hilus. 8 months later the hilar shadows were normal.	SR up to 60. Two lymph node biopsies equivocal; the third was definitely sarcoid.
5	Accentuation lung markings throughout, particularly both hila. Later peribronchial parenchymal mottling.	SR up to 28. Early negative tuberculin tests became positive. Elevated serum protein due to hyperglobulinemia. Lymph node and muscle nodule biopsies—sarcoid.
6	Enlarged peritracheal hilar node on right, enlarged left hilar shadow. Later, further widening of the hilar shadows.	SR up to 15. Two lymph node biopsies—sarcoid.
7	Bilateral enlargement of hilar nodes.	SR up to 23. Elevated serum protein due to hyperglobulinemia. Lymph node biopsy—sarcoid.

remained so for varying periods of time thereafter. In the third patient a determination was never made, and in the sixth it was never above 15. Neither of these patients had fever while in the hospital. In one, the first, the rate became normal just before discharge, though he never had fever. In two patients (patients 2 and 4) the sedimentation rate became normal before the disappearance of fever. In two others (patients 5 and 7) it remained elevated until the time of disposition, though both had been without fever for three months preceding. It may be of significance that in these latter two instances the disease was manifestly progressive throughout our study.

From a diagnostic standpoint, the laboratory procedures were of greatest aid in excluding disease for which specific tests are available. An elevated serum protein with hyperglobulinemia may well prove to be a constant feature, but our experience is only suggestive. In the light of present knowledge, the final diagnosis must be made, and can usually be made with assurance, by histological study of a biopsy specimen. In all of our cases an enlarged lymph node was the specimen removed. In one instance, four successive biopsies in nine months were required before the characteristic histological lesion was found, and in another a biceps muscle nodule provided the diagnosis we sought. However, a later lymph node biopsy in this patient did show sarcoid. In patient 5 lymphadenopathy was not conspicuous, but when it was finally appreciated that his chronic corneal lesions had first

TABLE III

Case	Admission Diagnosis	Subsequent Diagnoses				Disposition
1	April 22, '44 Chronic lymphadenitis				May 1, '44 Boeck's sarcoid	Nov. '44 Civil life
2	April 27, '44 Medical observation	May 4, '44 Rheumatic fever			July 11, '44 Boeck's sarcoid	Sept. '44 Civil life
3	May 4, '44 Lymphadenopathy	June 1, '44 Tuberculosis, lymph node			Aug. 17, '44 Boeck's sarcoid	Sept. '44 Civil life
4	April 10, '44 Rheumatic fever				March 22, '45 Boeck's sarcoid	Mar. '45 Civil life
5	May 3, '45 Catarrhal fever	May 4, '45 Mumps	May 4, '45 Catarrhal fever	July 8, '45 Active pulmonary tuberculosis	Nov. 2, '45 Boeck's sarcoid	Mar. '46 Transferred to VAF
6	February 12, '45 Medical observation	February 12, '45 Possible Hodgkin's disease	July 9, '45 Active pulmonary tuberculosis		Nov. 16, '45 Boeck's sarcoid	Dec. '45 Civil life
7	April 9, '45 Pseudohypertrophic muscular dystrophy	May '45 Progressive muscular dystrophy	July 5, '45 Active pulmonary tuberculosis		Nov. 23, '45 Boeck's sarcoid	Dec. 12, '45 Death

appeared in association with a bilateral parotitis (uveoparotid fever of Heerfordt) an epitrochlear node was found, removed, and proved to contain the lesion of sarcoidosis. Lymph node biopsy is necessary and usually accurate in the diagnosis of this disease. One should exhibit no more hesitancy in its use, even in repetition, than one does in making repeated studies on the blood in cases of diagnostic confusion.

Table 3 summarizes the diagnoses suggested. Through the diagnoses recorded in the course of the patient's illness one can visualize the clinical picture confronting the physician, and to some extent the clinical progress of the disease.

Five patients were discharged in the belief that the disease had become inactive. It is generally accepted that many spontaneous cures occur, even

after one or more relapses. Patient 5 was transferred to a Veteran's Hospital for continued observation because of signs of progression, in the absence of symptoms. The abbreviated data of the tables do not quite tell the story. One of his earliest symptoms was parotid swelling, diagnosed as mumps, which subsided promptly. His presenting symptom for the following six months was a migrating muscle soreness, which came to involve all voluntary muscles. Coincidentally, one could find in every palpable muscle innumerable small firm nodules, not unlike capsules, such as are used in oral medication. There was continuous fever and an elevated sedimentation rate. After six months fever and muscle soreness ceased but three other features now became prominent, in spite of the fact that the patient felt greatly improved. Both parotids became persistently enlarged and firm; a bilateral iritis appeared, with involvement of the posterior surfaces of each cornea. Roentgenograms of the chest revealed a peribronchial mottling within the lung parenchyma. Obviously the disease was active and progressive in spite of the patient's improved well-being. The sedimentation rate continued to be elevated until the date of transfer. One is inclined to believe that this patient will eventually succumb to his disease, even as patient 7. Both of these patients had widespread lesions of sarcoidosis, and both continued to have elevated sedimentation rates throughout the period of observation. In four patients the sedimentation rate became normal when the clinical signs of activity ceased. This suggests that an increased sedimentation rate may be an accurate measure of the activity of this disease.

The record of patient 7 will be presented in detail. The clinical story is interesting though not unique in the annals of recorded cases of Boeck's sarcoid. His sudden and unexpected death is sufficiently rare to warrant recording in its own right.

A negro, age 31, was first admitted to the sick list on April 9, 1945, with a diagnosis suggested as pseudo-hypertrophic muscular dystrophy, and complaining of anorexia, weakness, and pain in the calves of the legs for two months. He had previously been well. The pain had been throbbing in character, and there was associated numbness in the hands and feet. Examination was not remarkable save for evidence of weight loss of 16 pounds, and a generalized muscular atrophy. In May the diagnosis was changed to progressive muscular dystrophy. At this time he developed an acute swelling of both parotid glands. A roentgenogram disclosed no salivary calculi. This swelling subsided within three weeks, but during its course a bilateral iritis made its appearance, to become chronic in both eyes. The leukocytes numbered 5600 with a normal differential; the sedimentation rate was 6, the tuberculin skin test was negative in two strengths, and there were no acid fast bacilli in the sputum. Chest roentgenogram showed bilateral enlargement of the hilar nodes, thought to be tuberculous. On this evidence, and in the belief that the iritis might be from the same cause, the diagnosis was changed to active pulmonary tuberculosis and the patient transferred to this hospital. Here the blood cell counts and smears were consistently normal, but the sedimentation rate was found elevated to 20 to 30 upon repeated occasions until death. From July 11 to September 5 there was a daily fever of one degree, but none thereafter. Acid fast bacilli could not be found upon repeated examinations of sputum and gastric washings. Roentgen studies demon-

strated both hilar shadows to be unusually wide, with calcification within them; the left costo-phrenic angle was blunted and thickened pleura extended upward to the left apex along the lateral chest wall. The Mantoux test was negative in both strengths. Bronchoscopy on August 24 gave evidence of extrinsic pressure on the left bronchus. In August the ophthalmologist reported conjunctival injection in each eye and slight pupillary involvement. The slit lamp revealed a few keratitic precipitates on Descemet's membranes and the aqueous clear. The opinion was expressed that these lesions were not tuberculous in origin. In October roentgen therapy was directed to the hilar regions for diagnostic purposes, but no change in the shadows resulted. In November, while reviewing this man's entire record, it suddenly dawned on us that the simultaneous occurrence of parotid swelling and iritis five months earlier probably represented an uveoparotid fever of sarcoidosis. An enlarged epitrochlear node was removed, and the diagnosis of Boeck's sarcoid established on November 23.

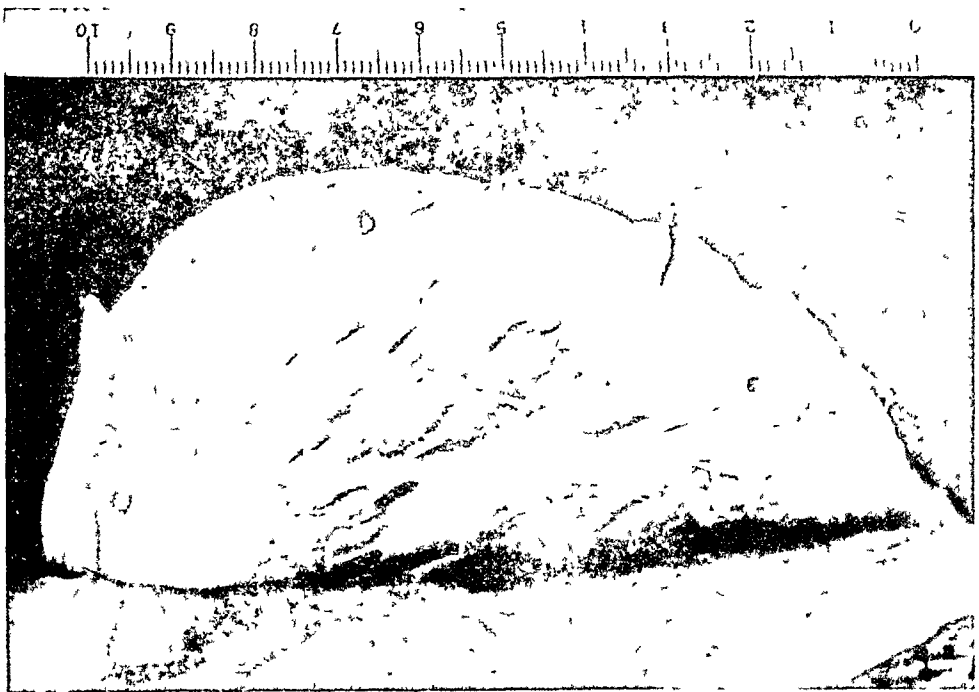


FIG 1. Myocardium of left ventricle invaded by sarcoidosis.

On the same date the plasma protein was found to be elevated, the increase due to a hyperglobulinemia. The ophthalmologist now described the eye lesions as follows: Bilateral circumcorneal injection with infiltration of Descemet's membrane in the right eye. In the left, punctate spots were distributed over the posterior surface of the cornea. Considerable pigmentation of the anterior lens capsule on the right. The patient felt and appeared to us perfectly well, except for the distress of the progressive lesions in the eyes. While making arrangements for travel on Christmas leave, he fell dead in a telephone booth.

Postmortem examination was made four hours after death. The body was that of a well nourished colored male, age 32, weighing 175 pounds. Each pupil measured seven millimeters in diameter. The sclerae were obscured by a hazy gray membrane. The corneal and conjunctival vessels were dilated and there were flame shaped hemorrhages radiating from each pupil. Within the thoracic cavity the visceral pleura was

adherent to the entire chest wall, the diaphragm, and pericardium. The right lung weighed 500 grams. Its pleural surface was studded with raised discrete, bluish nodules, five millimeters in diameter. They appeared to arise in the parenchyma of the lung and project above the surface into the visceral subpleural space. The pulmonary vessels were free of emboli. The lung parenchyma contained the same type of nodules, was air containing, and showed no caseation or cavitation. The left lung weighed 520 grams and was similar in appearance to the right lung. The hilar lymph nodes were greatly enlarged, discrete, and hard. The pericardium and epicardium were grossly normal. A peculiar tumor-like infiltration of the myocardium was evident in the walls of both ventricles, the interventricular septum, papillary muscles, and the base of the aortic valves (figure 2). These infiltrations were circumscribed, irregularly shaped, and pale yellow. The valve leaflets appeared normal, and the coronary arteries were free of occlusive or degenerative changes. Within the aorta

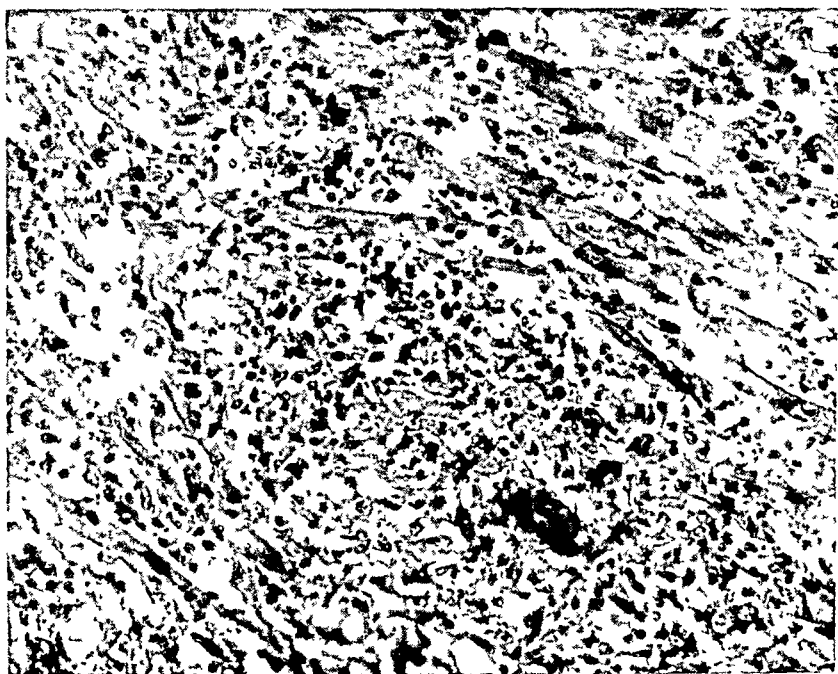


FIG. 2. Myocardium. Earliest lesions are at lower left. Older lesion is in the center.

were a few arteriosclerotic plaques. The spleen weighed 220 grams. The capsule was slightly wrinkled and within the parenchyma were many discrete, oval, gray tubercles. Both kidneys were of normal size and their capsules stripped with ease. No gross changes were noted in the kidneys, ureters, or bladder. The gastrointestinal tract was normal. Enlarged mesenteric lymph glands were present. The liver weighed 1200 grams and appeared normal, as did also the pancreas, adrenals, testicles, prostate, thyroid, and brain. Restrictions did not permit the removal of the eyes or parotid glands.

Microscopic examination of the scattered lesions in the lung parenchyma demonstrated that they were single and confluent masses of epithelioid cells containing many large multinucleated giant cells. There was no evidence of caseation, necrosis, or cavitation. Acid fast staining of the tissues failed to reveal tubercle bacilli. There was no zone of peripheral inflammatory reaction, but rather a concentric zone of collagen about most of these lesions. The giant cells were large and less regular than

those seen in tuberculosis, and many contained inclusion bodies of various types. Examination of the sections from the ventricles, interventricular septum, papillary muscles and epicardium revealed extensive replacement of normal tissue by a diffuse sarcoid infiltration. Most of these lesions were confluent, suggesting an inflammatory invasion of tissue with succeeding fibrosis. Lesions of all ages and types were present. The youngest ones consisted mainly of infiltration between intact and fragmented muscle bundles by epithelioid cells, plasma cells and lymphocytes. The oldest showed destruction and replacement of muscle by fibrosis with bordering collagen formation and a diminution in the number of cellular elements. Numerous large giant cells were seen scattered in irregular fashion throughout the granuloma. Many of these cells had inclusion bodies. The liver had single sarcoid tubercles scattered throughout the parenchyma, situated in the portal triad areas. The kidneys, spleen, tracheobronchial lymph nodes, and voluntary muscles all contained similar sarcoid tubercles, but the mesenteric lymph nodes, adrenals, pancreas, brain, meninges, and bone marrow did not.

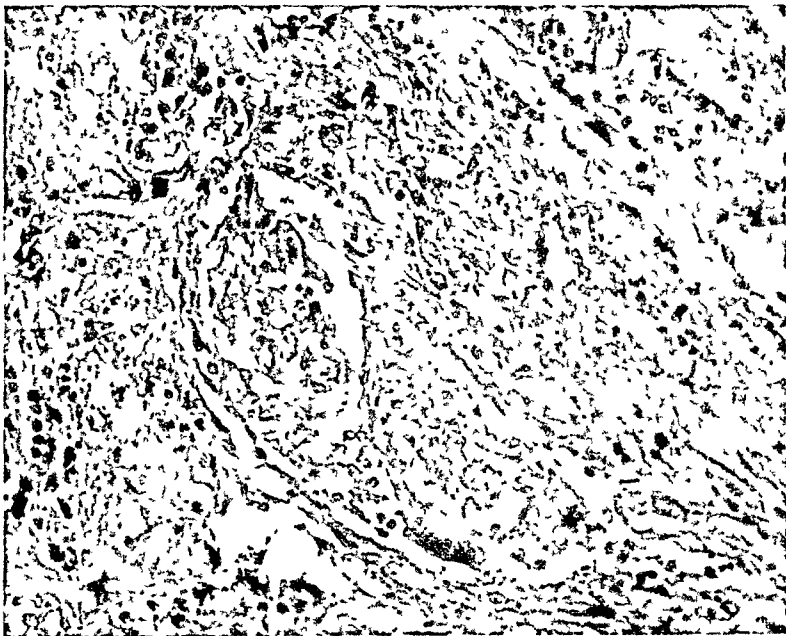


FIG 3. Myocardium. Older lesions and diffuse fibrosis are shown.

Descriptions of sarcoidosis of the heart made from postmortem observation are rare. Preceding ones have been published by Bernstein,<sup>2</sup> Schaumann,<sup>3</sup> Nickerson,<sup>4</sup> Spencer and Warren,<sup>5</sup> Cotter,<sup>6</sup> Longcope,<sup>1</sup> Johnson and Jason.<sup>7</sup> Before death in this patient there was no suspicion that the heart might be invaded by sarcoid. There were no symptoms to suggest it. The cardiac silhouette was not enlarged. The heart sounds were not thought to be abnormal. No electrocardiographic record was made. However, one sign was present to which more weight should have been given. The patient maintained a pulse rate of 90 to 120, even when afebrile. In reviewing the records of the other six patients in this series, we find the same elevated pulse rate obtained in patients two and five. The former was



dismissed as well. The latter, as previously noted, has a widespread and progressive form of the disease. An ECG tracing made just before his transfer to another hospital showed an elevation of the S-T segment in CF<sub>1</sub>, 2, and 3, with inversion of the T<sub>4</sub>, particularly marked in CF<sub>1</sub>. These changes were interpreted as evidence of invasion of the myocardium by sarcoid. Knowing that the myocardium may become a site of sarcoidosis without producing symptoms and that it may result in unexpected death, one dare not ignore a persistent tachycardia for the warning it may be.

In our patient, there were extensive lesions of all ages and types in the myocardium, including the interventricular septum and the epicardium. The youngest consisted of an infiltration of lymphocytes, plasma cells, and

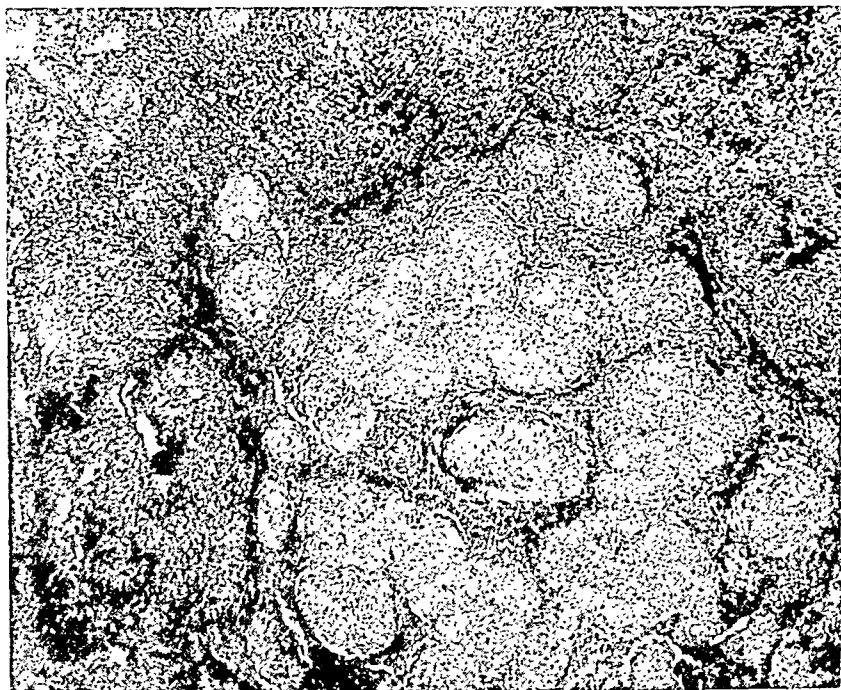


FIG. 4. Lymph node shows classical lesions of sarcoidosis.

macrophages into the myocardium between the muscle bundles. Older lesions showed more of the classical picture associated with sarcoidosis, mainly, a destruction of the myocardium with the site of the muscle bundles occupied by large pale staining mononuclear epithelioid cells and giant cells together with a moderate amount of collagen (figure 2). In the oldest lesions the epithelioid cells were replaced by fibroblasts and fibrocytes with resulting scarring (figure 3). Injection of macerated tissue from this case failed to produce tuberculosis in the guinea pig.

Grossly, the lesion of sarcoidosis appears the same in all organs, except that in the lung it may take on a bluish color from deposition of inhaled carbon pigment. Generally, it appears as a sharply circumscribed, oval or irregularly shaped, gray or yellow mass from one to 25 millimeters in diameter.

It cuts with ease and does not exhibit calcification. It has a hard and fleshy feel, and never shows cavity formation or caseation. Microscopically, the sarcoid tubercle exhibits a characteristic picture which may vary slightly with the age of the lesion, but is sufficiently unique to be recognized quite readily. It consists of masses of large, pale staining epithelioid cells usually surrounded by a concentric zone of collagen fibers. The lesions may be single or confluent and frequently exhibit a mosaic pattern (figure 4). The tubercles are usually devoid of a peripheral inflammatory zone, polymorphonuclear leukocytes are absent, and central necrosis is not seen. The giant cells associated with sarcoidosis are usually larger and more irregular in shape than those seen in tuberculosis, frequently have more nuclei (up to 30)

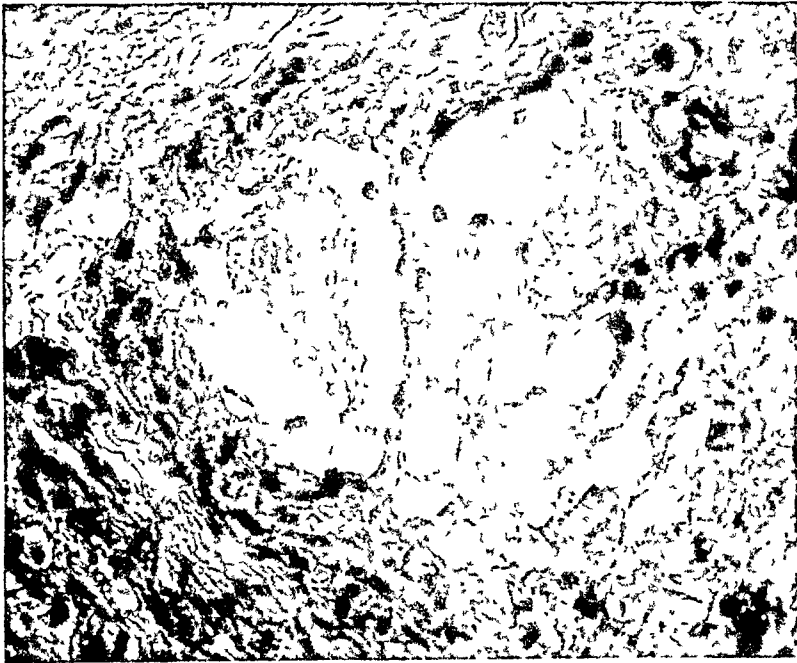


FIG. 5. Asteroid inclusion body in lymph node from patient who had no evidence of sarcoidosis.

and often show inclusion bodies of various sizes and shapes. The Schaumann type of inclusion body is usually seen as an oval shaped mass with concentric laminations, and may show yeast-like budding. This type often appears calcified and at times may reach a size larger than its parent giant cell. Friedman<sup>8</sup> describes asteroid inclusion bodies as large spheres, many of which show sharp pseudopodia protruding from the surface. He believes that different stages in the age of the asteroid body can be differentiated and that the younger forms are those which show a clear or punched-out area resembling a vacuole which often has a tiny pink staining sphere or coccoid body in the center. The diagnostic worth of asteroid inclusion bodies is debatable. The authors have seen asteroid bodies in giant cells in lymph nodes removed

from patients having no clinical, laboratory or histological evidence of sarcoidosis (figure 5). The histological structure of the "hard" tubercle must include reticulum fibers. These are usually present in the center of the sarcoid tubercle, but are absent in the tubercle of tuberculosis.

The criteria for a positive histological diagnosis of sarcoidosis proposed by Nickerson<sup>4</sup> are as follows: (1) Caseation must never be present. (2) Caseating tuberculosis should not be found anywhere in the body. (3) Reticulum fibers should be present in the hard tubercle. (4) Polymorphonuclear leukocytes must not be present. (5) Giant cells must be larger than those seen in caseating tuberculosis, they must contain more nuclei and

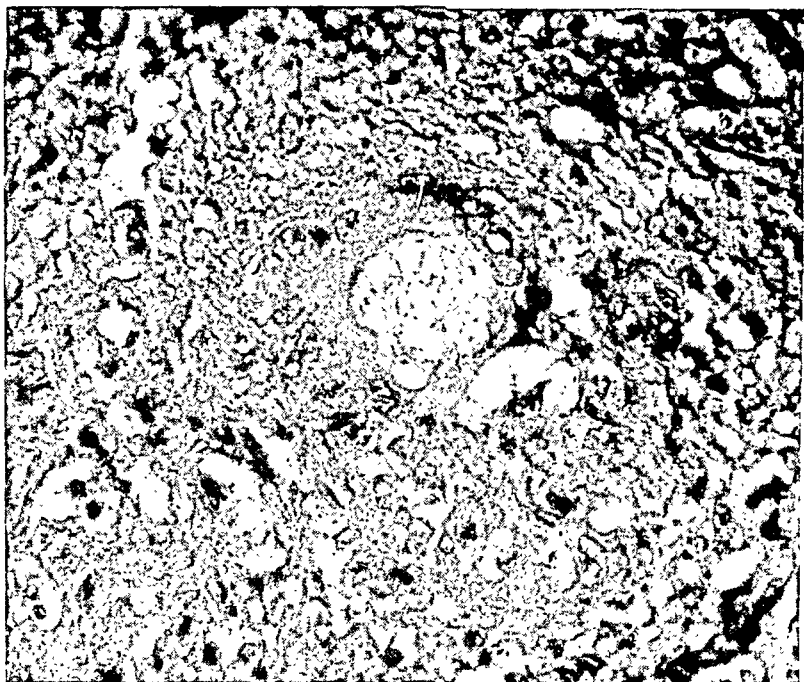


FIG. 6. Sarcoid tubercle of spleen. Giant cell shows vacuoles and coccoid sphere in its center.

the nuclei should be dispersed throughout the cytoplasm.<sup>6</sup> Lesions in the liver should be situated in the portal triad areas rather than mid-zonal, as in caseating tuberculosis. (7) Carbon pigment must not be present in extrapulmonary lesions. To these criteria it is suggested that another be added: One of the various types of giant cell inclusion bodies must be present. This would serve further to protect from confusing the sarcoid tubercle with that of tuberculosis. However, it is felt that these histologic criteria must be combined with the clinical picture of sarcoidosis before one can be absolutely certain of the diagnosis in debatable cases. It is believed that the finding of tuberculosis somewhere in the patient's body does not necessarily rule out the presence of concurrent sarcoidosis.

Our purpose has been simply to call attention once again to this little known, little understood disease, which has been best described as a benign lymphogranuloma. To that end the clinical records of seven patients with Boeck's sarcoid have been briefly reviewed, and the postmortem observation findings in a patient who had an extensive sarcoidosis of the myocardium have been discussed. In conclusion, these comments are set forth:

1. Widened hilar shadows seen in the roentgenogram are a common and early accompaniment of Boeck's sarcoid.

2. An elevated serum protein and hyperglobulinemia may serve to suggest the diagnosis of Boeck's sarcoid.

3. Biopsy provides the only certain method of identification of sarcoid. An accessible lymph node will always eventually provide the necessary specimen.

4. The histological features of sarcoid are definite and usually unmistakable.

5. An elevated sedimentation rate may be an accurate measure of the activity of this disease.

6. A persistent tachycardia should be a warning that the myocardium has been invaded by sarcoidosis.

#### BIBLIOGRAPHY

1. LONGCOPE, W. T.: Sarcoidosis, or Besnier, Boeck-Schaumann disease, Jr. Am. Med. Assoc., 1941, cxvii, 1321.
2. BERNSTEIN, M., KONZELMANN, F. W., and SIDLICK, D. M.: Boeck's sarcoid: report of a case with visceral involvement, Arch. Int. Med., 1929, xlv, 721.
3. SCHAUAMANN, J.: Boeck's sarcoid, Brit. Jr. Dermat., 1936, xlviii, 399.
4. NICKERSON, S. A.: Boeck's sarcoid: report of six cases in which autopsies were done, Arch. Path., 1937, xxiv, 19.
5. SPENCER, J., and WARREN, S.: Boeck's sarcoid: report of a case with clinical diagnosis confirmed at autopsy, Arch. Int. Med., 1938, lxii, 285.
6. COTTER, E. F.: Boeck's sarcoid: autopsy in a case with visceral lesions, Arch. Int.-Med., 1939, lxiv, 286.
7. JOHNSON, J. B., and JASON, R. S.: Sarcoidosis of the heart, Am. Heart Jr., 1944, xxvii, 246.
8. FRIEDMAN, M.: Sarcoidosis of the spleen. Report of a case with autopsy and a study of intercellular "asteroid bodies," Am. Jr. Path., 1944, xx, 621.

## CHANGING CONCEPTS OF DISEASE \*

By KARL MENNINGER, M.D.,† *Topeka, Kansas*

IN deciding what I as a psychiatrist might present to this representative body of internists, I considered several possibilities. I could talk about something which I understood fairly well but with which you are less familiar, such as the psychodynamics of schizophrenia. This might impress you with my expertness, but it would also probably puzzle you. Or I could talk about something which you know all about and I very little about, and this would amuse you. I could talk about something which we all know about, and this would bore you. So I concluded to talk about something which neither of us know much about, hoping that this might at least intrigue you.

So I begin by assuring you that I am well aware that I know almost nothing about the subject I am presenting except that it is important for us all to think about it.

Perhaps I can enlist your interest in the topic if I recite briefly how I came to begin thinking about it. I have said that I was a psychiatrist. So I was for over 25 years. Recently, however, I have had to become a physician! In my position as director of a graduate school of medical education which includes young surgeons and young internists as well as young psychiatrists; and also in my capacity as director of a sizeable general hospital, I have had to think of medicine as a whole. I have had to try to relate in principle and in practice the functioning of many different kinds of doctors. I have had to revise my comfortable notions about a lot of things which we doctors get into the habit of taking for granted.

For example, I used to think that the accepted formula for any properly trained medical man was very simple—collect data about a patient, organize them, establish a diagnosis, and treat the patient according to the diagnosis. Examination, diagnosis, treatment; patient gets well and lives happily ever after (unless, of course, an error has been made in the diagnosis!)

I am somewhat ashamed to say that it has taken me a quarter of a century to realize that this formula rarely works out this way in actual practice and that it may well be that it is the wrong formula.

What I got out of medical school was the conviction that the world was full of healthy human beings, and that now and then a victim was struck down by a cruel blow from an unheeding Nature—an infestation, a lurking bacterium, a malignant cell. Now and then an inexplicable perversity seized the liver or the pancreas or the bone marrow. As a result, a “disease” de-

\* Presented before the Twenty-Ninth Annual Meeting of the American College of Physicians, San Francisco, April 19, 1948.

† Manager, Winter Veterans Administration Hospital; and General Director, Department of Education, Menninger Foundation, Topeka, Kansas.

veloped and a patient appeared on the doorstep of the physician. With the proper questioning and the proper application of a few indispensable gadgets, the diagnosis was correctly established and the proper treatment instituted.

It never occurred to me in those days to realize that *most* people in the world are sick, and not the exceptional individual who came to the Out Patient Department of the Massachusetts General Hospital. It never occurred to me in those days that the pain produced by a sickness might be experienced by everyone else in the patient's environment more than by him. It never occurred to me to consider how much society determined the illness of a particular individual or how much the individual himself determined, desired, and even inflicted upon himself the suffering for which I as a physician was asked to offer relief. Disease, as I viewed it, and I think I fairly accurately caught the spirit of my preceptors, was an entirely unwanted, useless, purposeless misfortune, acquired inadvertently through an unfortunate concatenation of forces emanating from the best of all possible worlds or from the defective architecture of an hereditary constitution.

It is not often that we discuss the basic philosophical assumptions of medicine, and perhaps most of my audience has been so engrossed, as I have, in doing the daily job with the presenting patient, that we haven't stopped to reflect, as I had to in writing this paper, how much our daily experience has taken us away from such concepts. Don't we all agree, really, that whether we call them psychiatric problems or psychosomatic problems or allergic problems or cardiovascular problems or something else, most of the patients—far and away the majority of patients—that you and I treat day after day cannot be given an accurate, specific, meaningful diagnostic label and do not represent any disease entity?

What shall we call the "disease" represented by a man who has always been frail but has worked very hard to support his widowed mother, did not feel he could afford to get married, buries himself in the details of a complicated job, develops paralyzing headaches, loses time at the office for which pay is deducted from his wages, worries about this so much that he loses sleep and begins vomiting after each meal? Just to make it complicated, he has a leukocytosis and an enlarged spleen. Does not such a case defy diagnosis?

Even in the simplest cases it seems to me misleading to make a diagnosis in the old-fashioned way. A middle-aged puritan spinster appears in my office with a chancre on her lip. Isn't this a simple diagnosis? I don't think so. Nor would you if I told you the circumstances of how she acquired that chancre, whom she acquired it from, how she happened to select that type of man, or why she permitted him to kiss her. Her sickness cannot be accurately diagnosed just as syphilis. She did not come to me because of it. What she came to me for was a more serious thing. She was so depressed about the implications of the infection that she now wanted to kill herself. What is the name of that disease? Is it a part of the syphilis?

The doctor who is giving her penicillin was wise enough to know that penicillin alone would not cure her.

Diagnosis in the sense in which we doctors have used it for many years is not only relatively useless in most cases; it is an inaccurate, misleading, philosophically false predication. Many doctors know this intuitively. When patients ask, "What is this that has gotten me down?" such doctors reply, "Oh, its a respiratory thing," or "Apparently you caught a bug that is going around"; or "You have a cardio-vascular involvement; it's tied up with this worry you have at present. Your blood pressure isn't dangerously high and your heart's making an adjustment to it. I think things will improve when that contract is signed." These are not diagnoses in the old sense; they are evasions of diagnosis. Such doctors might be embarrassed if we pressed them, and I think we have no right to do so because these doctors feel the untruthfulness, the unscientific nature of a diagnosis according to our former schedules. We used to think that a doctor who indulged in such vagueness was an unscientific doctor, that all that was the matter with American medicine was the failure of "the old fellows," as we patronizingly called them, to see the necessity of establishing a diagnosis as a basis for treatment. Of course, there was a certain truth in this, and there was also a certain great falseness in it and it is the falseness that I want to examine today.

I realize that throwing doubt upon the desirability of making a diagnosis as I have done is bound to be disturbing to many physicians. "Granted," they will say, "that one finds many cases in which he cannot make a diagnosis and many in which he has to make a multiple diagnosis, the fact remains that we ought to try to decide what is wrong before we plunge wildly into some kind of therapy. You are attacking a basic foundation stone in scientific medicine. You are encouraging eclecticism and opportunism and shotgun therapy. You are going against everything that we have spent hundreds of years trying to establish."

No, I am not; really I am not. I suffer from the same uneasiness that you do about the consequences of a misinterpretation of what I am saying. But I ask you to listen carefully: *I have not said that* we should not attempt to make a diagnosis. I have merely said that this simple formula of *diagnosis determines treatment* can no longer be carried out as we originally conceived of it, because diagnosis is too complex and attempts to make it simple and definite lead us into error. I have given you some cases to illustrate this and I shall give you some more.

A travelling salesman of 25 had kept at his job for several years in spite of an increasingly extensive exudative and distressing dermatitis. He had had all sorts of treatment for it, to no consistent avail. Because of it he felt unable to make proper social contacts and feeling increasingly excluded from the company of "nice girls" he felt obliged to force his attention upon prostitutes. When even prostitutes were dismayed at his appearance he

convinced himself that his sexual life would have to be a choice between masturbation and rape.

About this time he was inducted into the Navy and after about a year of unsatisfactory service, he was discharged. In his own words, "I guess I just scratched myself out of the Navy." He then proceeded to scratch himself into another hospital, where I saw him.

Everything else having failed, the man was quite willing to see a psychiatrist and proceeded to take advantage of the doctor's invitation to tell him all about his problems. He talked on and on; and the psychiatrist listened on and on. He became intensely emotional in his recollection of the various complications of his life; for the first time the entire pattern began to unroll. The psychiatrist continued to be attentive, permissive, and non-committal.

And now what do you think happened? Having thus relieved himself of guilt feelings, shame, fear and other stored-up emotion, the patient recovered; his dermatitis disappeared? Not so; it promptly became very much worse! Somewhat disturbing to the notion that psychosomatic afflictions can be deftly cured by emotional catharsis, isn't it?

We doctors are all only too painfully aware that our most logical and best intended treatments often make patients worse instead of better. It is a blunder we all make; it derives in part from the fact that we cling to an outmoded practice of making disease-picture diagnoses. This leads to a treatment regime based not on the patient's condition, not on his real disease, but on the preconceptions of the particular person who sees the patient. In the case of the clerk which I related first, the sociologist would make a diagnosis of bad labor conditions, the internist might make a diagnosis of anorexia nervosa, the neurologist might see it as an aggravated migraine. In the case of the young girl, the syphilologist made a diagnosis of syphilis, and the psychiatrist a diagnosis of melancholia. In the skin case just related, five different diagnoses had been made—sexual psychopathy, vocational ineptitude, several kinds of dermatitis, and conversion hysteria.

"Very well," you will say, "perhaps he had all of these; multiple diagnosis is all right. But we must have diagnosis." Yes, but the question is, who is the "we"? Do you mean we internists? we neurologists? we pathologists? we sociologists? we psychologists? we psychiatrists? All of us are interested in the same individual; we all believe in the same scientific laws; we are all studying the same interrelated phenomena. Yet, each of us has our own little list of syndromes and we look for symptoms to fit a preconception without reference to any other "we," and call that a diagnosis. And just as surely as we do that, we violate the basic principle of the modern holistic or totalistic concept of the human organism. In theory there cannot be any such thing as a simple, uncomplicated diagnosis of anything, not even measles. The child with measles has at the same time some educational interruptions, and some social complications, and some disturbed



relationships with parents and siblings. The only scientific right that we doctors have to so label the total situation in which a school child goes home sick with "measles" is the practical usefulness of a term, the full implications of which are fairly familiar to the general public. Any case of measles is far more than measles, any case of syphilis is far more than syphilis, any case of dermatitis is far more than a skin rash.

If, then, there is some practical advantage in adhering to conventional labels, and if in the back of our minds we remember that the total human organism is a physical-chemical-social-psychological interacting unit, what is the harm in continuing to use these convenient medical handles?

In many instances, none—provided we realize that any such diagnosis is a misnomer. But the tendency is to forget this and to assume that sick patients can be treated like automobiles—properly labelled and then passed down an assembly line of specialists for a punch here and a wrench there—without the guiding principle of an overall perspective.

I recall a young banker in a small Wisconsin town who had built up his bank from a hard start by dint of assiduous application and good judgment. He began to suffer increasingly from indigestion and his family physician, who was a member of the Board of Directors of the bank, studied him in the appropriate medical way and made a diagnosis of peptic ulcer. For a matter of eight years dietary and medical treatment kept the pain under control, but as guardian of the health of one of the community's most important citizens his family physician was disturbed by the possibility of hemorrhage, perforation, or chronic invalidism. He had repeatedly urged upon the banker the advisability of surgical treatment. The patient had strenuously resisted. Finally the conscientious doctor insisted upon the operation, and a successful gastrectomy was skilfully performed. He made an uneventful recovery and returned home.

But he did not return to work. He had become depressed. He appeared physically well, but he felt melancholy, pessimistic, unable to take interest in his work, his customers or his friends. Month after month passed and his depression deepened rather than lifted. His very much worried family physician now urged that he go to a sanitarium. To this the patient demurred. Finally under the pressure of friends, family, fellow citizens and doctor, he agreed to go.

While his wife and his physician were making preparations to carry out this plan, the patient committed suicide.

To this day that family physician doesn't understand that tragedy. He keeps wondering what he did wrong. According to our false principles of departmentalized diagnosis and *ad hoc* treatment, he did nothing wrong. The patient had an ulcer and he received appropriate treatment for that; then the patient perversely developed depression and the doctor arranged the appropriate treatment for depression. It never occurred to him that the patient's ulcer was not his disease, depression was not his disease. His dis-

ease was something defective in his total life adjustment. While the bank was struggling he had no physical symptoms, but he had worry; when the bank got on its feet he had no worry, but he developed gastric pain. So long as he had gastric pain, his life adjustment remained in balance. But when this source of suffering was taken away from him he developed another type of suffering and when this final type of suffering was threatened with removal, he killed himself.

What was "the disease" of that banker?

What is the diagnosis in a patient who has coronary symptoms whenever he takes his wife to a party? or in a woman who has migraine on the week ends that her son is home from college?

What kind of arthritis is it which becomes activated with each quarterly meeting of the board of directors?

If a young wife's dysmenorrhea disappears when her husband is drunk, or if a child vomits each morning just before school time, or if an educated young Negro trying to establish himself in a decent business in an average American city develops vascular hypertension at 35, or if the mother of five children who has been working an 18 hour day starts coughing up a little blood, or if a man reared in a home where the drunken father regularly abused his family develops syncope when he goes to his employer's office, or if a rugged individualist who believes in free enterprise exhibits his belief by bullying his employees five days a week and concealing his own feelings of insecurity by week ends of alcoholic anesthesia—if these patients come to see us, as they do every day of the world, what shall we say the disease is, in each case? What are the diagnoses? And what conceivable relationship do any medical diagnostic terms we might apply to them have to the necessary treatment programs?

We cannot make diagnoses to fit such disease pictures as these because our medical diagnostic categories depend upon traditional formulations some of which date back to pre-historic times. Seguin of Peru has, in a recent brilliant article,\* called the bacteriological era of medical history the "Golden Age for the demoniac concept of disease, when germs became the scientifically named demons." In giving temporary support to the fallacious causality principle, the discovery of bacteria vastly retarded progress in our scientific medical thinking. Every thoughtful person knows that no thing or event in the world can have a cause, and that while the impulse to seek causes is, as Tolstoy says (in *War and Peace*), innate in the soul of man, "the combination of causes of phenomena is beyond the grasp of the human intellect." The early Greek physicians knew this and concentrated not on causes but on the phenomena of disease—the symptoms. Rivaling this "phenomenological concept" were theological concepts which equated disease with sin or with punishment, and then the humoral concepts which later found some representation in endocrinology. Virchow fought against the

\* "Concept of disease," *Psychosomatic Medicine*, 1946, viii, 252-257.

*sedes morborum* concept of disease which had been crystallized by Morgagni, distinguished by great conflict between the humoralists just mentioned and the "solidists" who sought to locate the "seat of disease" in organs. But in the end Virchow himself fell victim to the very theory he was combatting by locating the seat of disease in the cell.

In common parlance we talk irrationally and childishly about the patient "fighting the disease," "facing it," "resisting it" and the like, forgetting that disease is not something external or alien but it is *of* the patient, and largely his own doing. The real problem is, what forces him to do it so? How have his defenses handled some new situation? And to what extent have those malignant self-destructive tendencies, which are in us all, combined with external forces to result in pain and faltering and sometimes death? It is somewhat shocking to read, even in some modern textbooks of pathology, statements which imply that disease is a *thing*, a horrid, hateful external thing, which invades the human organism like a snake in a dove's nest. Clinical medicine, with the fructifying stimulation of psychiatry and the psychoanalytic study of the unconscious processes, has a far more dynamic and progressive view than a pathology still couched in descriptive phenomenologic and demoniac terms.

For I believe that clinicians have come to think of disease more and more in terms of a disturbance in the total economics of the personality, a temporary overwhelming of the efforts of the organism to maintain a continuous internal and external adaptation to continuously changing relationships, threats, pressures, instinctual needs and reality demands. The concept of biochemical homeostasis of the organism, which Cannon so beautifully described, has been extended to include a recognition of a noncommittant and interrelated psychological homeostasis and sociological homeostasis, contributing to the total personality. The thoughts, feelings, behavior and social relationships of patients, no less than their tissues and their body fluids, follow the same principle, the principle of continuous adaptative shifts and reciprocal balances.

When any one of these elements is disturbed from within or from without, the recovery of balance is attempted through a readjustment of all the others. The *agent provocateur* may be bacterium or a bayonet, a cancer cell or a seduction, a starvation of calcium or a starvation of love. Whatever the upsetting influence, many elements coöperate to restore the balance. Sometimes they overdo it, and the last state is worse than the first. For some aspects of this imbalance we have medical terms, for some aspects we have only sociological or common speech terms. But a meaningful diagnosis cannot be confined to the terms of any one discipline. To do so is to mislabel the condition, to misconceive its essential nature. What we conventionally call "disease" is sometimes the *agent provocateur*, sometimes the wound; it is sometimes the overaction of systemic defense measures and sometimes the consequences of mismanagement by relatives, friends and

even doctors. It is sometimes the picture of a triumphant malignancy, and sometimes that of a quiet renunciation, the sacrifice of a part for the whole, as with Polycrates' ring. All these we have called "the disease."

*It is the imbalance, the organismic disequilibrium, which is the real pathology*, and when that imbalance reaches a degree or duration that threatens the comfort or survival of the individual (or his environment), it may be correctly denoted disease. The protean manifestations of that imbalance must be looked for by the doctor in all the spheres of human life, identified in their relationships, understood in their totality, recognized as symptoms of the imbalance, and labelled in any pragmatically useful way. But they must *never* be mistaken for "*the disease.*"

# THE ANIMAL KINGDOM, A RESERVOIR OF HUMAN DISEASE\*

By K. F. MEYER, M.D., *San Francisco, California*

THE everlasting questions "why epidemics" and "in what manner has the human race become subject to multiform epidemization" encouraged for over a span of 40 years and on three continents the quest for answers. With the improvement of investigative methods, disease entities due to hitherto unknown infectious processes have been identified. To be sure, the number is steadily increasing, and there is no reason to believe that the total has as yet been reached. In the course of the search, it became clear that the parasitic diseases of man and animals are obviously a part of a broad evolutionary development. Again and again it has been discovered that animals in nature and those subsequently domesticated are a potent source of human illness and death. Ever since man's existence, he has been brought into intimate relation with the "living environment." Not only have animals furnished him the food and raw products of various sorts which enable him to work and to defend his existence, but they have approached him as injurious and destructive enemies. How different today are the answers when a mammal or an invertebrate is found to be a carrier or vector of a microbial or viral agent pathogenic to man.

Although Hippocrates and Galen and Aristotle diligently compared the diseases of man and animals, and Virgil and Pliny described pestilence predominant in animals, and I. Virgil and Pliny described his knowledge of the spread of truth, and Fracastoro's vivid account of the transmission of rabies: "When the outer skin is so torn by the bite of a dog that blood is drawn and contagion takes place through contact with the teeth and foam from the mouth of the rabid animal" succinctly describes the relation of a disease of an animal to that of man. However, the highly religious attitude of the Middle Ages introduced a sharp distinction between the maladies of man and those of animals. While the Greek and Roman medical writers considered the similarity of disease processes in man and beasts, writers of the Middle Ages stressed the difference. Man, an image of God, could and should not be compared with the representatives of the animal kingdom!

Much later the discovery by Jenner that a disease of cows—cowpox—is related to a similar malady in man ushered in a new epoch. Aside from being a marvelous beginning because it furnished the basis for powerful protection against smallpox, it aroused, in the words of Jenner, great interest

\* Presented at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948.  
From The George William Hooper Foundation, University of California, San Francisco, California.

in "the prolific source of disease" that lingers in the animals of the forest "which may not originally have been intended for his associates." The new science began on top of a mountain, the benefits have been matched by subsequent achievements, but it is doubtful that the original crest will be surpassed. Leuckart's classical investigations in the middle of the nineteenth century demonstrated the significance of animal life cycles in human helminthic infections. The discovery of the presence of the parasite of filariasis in mosquitoes by Manson in 1879 and the first clear demonstration by Smith and Kilborne in 1893 that a protozoan disease of higher mammals is transmitted in a roundabout fashion by an intermediate host belonging to the group of the arthropods ushered in another epoch of phenomenal development. The application of the theory of the insect carrier led to the revelation of the secret of the tsetse fly disease, malaria, yellow fever, bubonic plague and typhus. A study of the ecology of the insect carriers or vectors involved far-reaching surveys of the animal kingdom. Totally unexpected situations came to light. Today the spread of the infections—rickettsial diseases, plague, encephalitides—from an ineradicable wild rodent or bird reservoir of infection is fully established. Fortunately, serious epidemics of these diseases can be suppressed by measures directed against the mosquitoes, the rats in cities and the lice on the human body.

### THE INFECTION CHAIN

The vast literature which deals with the newer knowledge of infection relationships is scattered throughout scientific journals and is not readily accessible to the clinician. To simplify orientation and to facilitate discussion, the essential facts have been summarized and tabulated under the heading "Heterogenous Infection Chains."

A brief explanation of this tabulation seems desirable.

Viewed by the naturalist, an infection is analogous to or identical with the *biological phenomena of parasitism* so widely existent throughout the animal and plant kingdoms. Until recently, the medically oriented microbiologist approached an infection from the standpoint not of the agent but of the altered state of the host—the disease. With the recognition of the so-called latent, inapparent or subclinical infections, and the infections without an infectious disease, this strictly utilitarian concept has been found untenable. The biologic definition of an infection as a host-parasite relationship offers a reasonable foundation on which to anchor the ever-growing store of knowledge. The transmission from host to host is incumbent upon all parasites; whether the transfer from the infected to the non-infected occurs directly or indirectly is immaterial. In principle, the relationship between the infection in the two hosts, one as "dispenser" and the other as "receiver," remains the same. One may conveniently designate the transmission from man to man or from animal to animal as a homogenous, and the transmission from an animal host to man or man to animal as a hetero-

genous infection chain. In table 1 the principal transmission chains are illustrated, and the known relationship of diseases of animals and man is elucidated by concrete examples. In the first paragraph the infectious diseases which may be conveyed from warm-blooded animals by the cutaneous, the alimentary or the mucosal aerogenic routes to man are listed. The name of the disease is followed by the species of animal which serves as the principal "dispenser" of the infective agent. This grouping is incomplete but it does comprise most of the known bacterial virus infections. In the last section the helminthic invasive diseases are considered. In order to avoid unnecessary confusion in the interpretation of an already complicated tabulation, the name of the bacterial or virus agent is usually omitted. Since this group embraces infections which are variable with respect to the disease incitant, mode of transmission, pathways of infection and epidemiology, it is possible to give but a few general characteristics which would equally describe all the representatives of the category.

The following facts are noteworthy:

(a) The diseases of highly organized mammals not only unfavorably affect the health of man, but through their serious economic effects also injure his welfare. Financial investment in animals is large; millions of

TABLE I

## Heterogenous Infection Chains

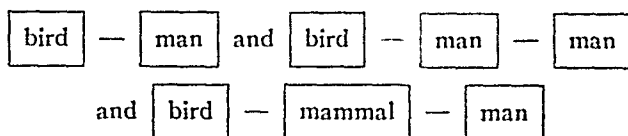
## Ia. Highly organized: Homeothermic manimals

animals	—	man	Passage usually broken
---------	---	-----	------------------------

- (1) Tuberculosis: Cattle
- (2) Brucella infections (a) Bang's disease: Cattle, hogs, horses, dogs?  
(b) Malta fever: Goats, sheep, hogs, dogs?
- (3) Salmonella infections: Dogs, cats, cattle, hogs, sheep, rats, mice
- (4) Swine erysipelas: Hogs, sheep?, [fish]
- (5) Anthrax: Cattle, sheep, hogs, minks, others
- (6) Plague: Wild rodents
- (7) Pasteurelloses (*Pasteurella multocida*): Cats, dogs, rabbits
- (8) Pseudotuberculosis: Cats, rodents?
- (9) Tularemia: Cotton-tail rabbits, other mammals
- (10) Glanders: Horses, mules
- (11) Melioidosis: Rats, cats, dogs, horses
- (12) Listerelloses: Cattle, rodents
- (13) Trichophytosis: Horses and cattle in rural areas, cats and dogs in urban areas
- (14) Rabies: Dogs, other carnivores, vampire bats, others
- (15) Foot and mouth disease: Cattle, hogs
- (16) Lymphocytic choriomeningitis: Gray mice, dogs?
- (17) Pernicious anemia: Horses
- (18) Virus B: Monkeys (*Macacus rhesus*)
- (19) Sore mouth: Sheep
- (20) Pox diseases—vaccinia: Cattle
- (21) Leptospirosis: Rats, mice, dogs, cats, pigs, foals, horses, foxes, cattle
- (22) Rat bite fever (*Spirillum minus*, *Streptobacillus moniliformis*)—Sodoku: Rats, mice
- (23) Balantidiasis: Monkeys, domestic pigs
- (24) Espundia (*Leishmania americana*): Dog, agouti (*Daryprocta*)
- (25) Q fever group (*Coxiella burnetii*): Cattle [aerogenic transfer? ticks?]
- (26) Toxoplasmosis (Toxoplasm): Mammals [arthropods?]

TABLE I—Continued

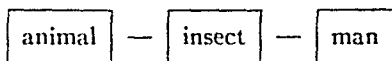
## Ib. Highly organized: Homeothermic birds



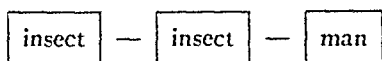
- (1) Tuberculosis: Birds, barnyard fowls
- (2) Psittacosis: Parakeets, South American and Australian psittacine birds, canaries, finches, fulmars, pigeons, chickens, ducks
- (3) Fowl pest—Newcastle disease: Barnyard fowls
- (4) Favus: Chickens
- (5) Salmonella infections: Ducks, turkeys, chickens, pigeons
- (6) Tularemia: Gamebirds
- (7) Toxoplasmosis: Birds

## II. Lowly organized: Arthropod vectors

## A. Mechanical transfer

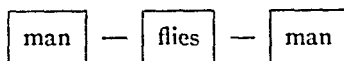
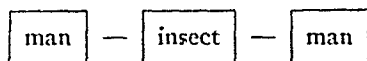
*Anthrax*

Vector: Biting flies (Stomoxys, Tabanus)

*Tularemia*Vector: Deer fly (*Chrysops discalis*)*Dermatobiasis (Dermatobia hominis)*

Vector: Psorophora—mosquitoes

## Subgroup 1

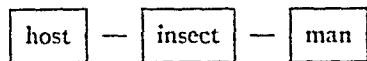
*Dysentery, cholera, typhoid, poliomyelitis*Vectors: *Musca domestica*, *Chrysomya megacephala*, *Aphiochaeta ferruginea*, *Phormia regina*?, *Phoenicia sericata**Yaws (Treponema pertenue)*

Vectors: Hippelates sp., Musca sp.

*Follicular conjunctivitis (virus)*

Vector: Hippelates sp.

## B. Cyclopropagative multiplication in vector

*Malaria (Plasmodium vivax, P. malariae, P. falciparum, P. ovale)*Vectors: *Anopheles freeborni*, *A. quadrimaculatus*, *A. punctipennis* in United States, *A. gambiae* in Africa, *A. pseudopunctipennis* in South and Central America, *A. punctulatus* in Polynesia, *A. subpictus* and *A. maculatus* in Java and Malaya

## Subgroup 2

*Trypanosomiasis (Trypanosoma gambiense, T. rhodesiense)*—African sleeping sicknessVectors: *Glossina tachinoides*, *G. morsitans* in Africa*Chagas disease (Trypanosoma cruzi)*Vectors: Reduviidae—*Mestor megistus*, *Triatoma infestans* in South America

Hosts: Dogs, cats, armadillos, pack rats

*Leishmaniasis (Leishmania donovani, L. infantum, L. tropica)*—Kala-azar, oriental sore, visceral and cutaneous leishmaniasisVectors: *Phlebotomus (P. major, P. perniciosus)*

Contamination—infection

Hosts: Dogs, gerbilles, ground squirrels



TABLE I—Continued

## C. Propagative multiplication in vector

man — insect — man

Yellow fever (virus, "amaril")—urban type

Vector: *Aedes aegypti*

Dengue (virus)

Vectors: *Aedes aegypti*, *A. albopictus*, *A. scutellaris*?

Sandfly fever (virus)

Vector: *Phlebotomus papatasi*

Relapsing fever (*Borrelia recurrentis*)

Vector: *Pediculus humanus*

Epidemic typhus (*Rickettsia prowazekii*)—classical typhus, old world typhus

Vectors: *Pediculus humanus*, var. *corporis* and var. *capitis* by fecal droplets

vertebrate host — insect — man

Yellow fever (virus)—rural type, jungle type

Primate-mosquito cycle

Hosts: Red howler (*Myctes seniculus*), marmosets (*Callithrix aurita*) in

South America, red-tail monkey (*Cercopithecus nictitans impangae*) in

Africa, other primates

Vectors: *Aedes leucocaelenus*, *Haemagogus capricorni* and *H. spegazzini* in

South America, *Aedes simpsoni*, *A. africanus* in Central Africa

Western equine encephalomyelitis (virus)

Principal hosts: Chickens, other birds

Vectors: *Culex tarsalis*, *Aedes dorsalis*, *Culiseta inornata*, *Triatoma sanguisuga*,

*Dermanyssus gallinae*?, *Liponyssus sylviarum*?, *L. bursa*?

Accidental hosts: Horses, mules, deer, hogs, prairie chickens, man

Eastern equine encephalomyelitis (virus)

Reservoir: Birds?

Vector: *Aedes*?

Accidental hosts: Horses, mules, pigeons, pheasants, man

St. Louis encephalitis (virus)

Principal hosts: Chickens, other birds

Vectors: *Culex tarsalis*, *C. pipiens*, *Aedes dorsalis*, *Culiseta*?, *Dermanyssus*

*gallinae*?, *Liponyssus sylviarum*?

Japanese B. encephalitis (virus)

Reservoir: ?

Vectors: *Culex pipiens*, *C. tritaeniorhynchus*, *Aedes togoi*?

Susceptible host: Horses

Enzootic hepatitis (virus)—Rift Valley hepatitis

Reservoir: Sheep, cattle

Vector: *Mansonia fuscipennatus*

Other virus infections (California, West Nile, Semiliki Forest, Columbian encephalitis viruses)

Possibly similar chains as others in this subgroup

Vector: Mosquitoes

Carrión's disease (*Bartonella bacilliformis*)

Reservoir: ?

Vector: *Phlebotomus verrucarum*

flea — rodent — man

and rodent — insect — man — man

and rodent — man — man

Plague (*Pasteurella pestis*)

Vectors: *Xenopsylla cheopis*, *Nosopsyllus fasciatus* on rats, *Diamanus montanus*, *Thrassis* sp., *Oropsylla* sp. and other sp. on wild rats, lice, ticks

Hosts: Rats (*Rattus norvegicus*, *R. alexandrinus*), ground squirrels (*Citellus* sp.), marmots and prairie dogs (*Cynomys* sp.), chipmunks (*Eutamias* sp.),

squirrels (*Sciurus*), native rats and mice (*Neotoma* sp., *Microtus* sp.)

TABLE I—Continued

Subgroup 6	rat — flea — man — louse — man
	and rat — mite — man — <span style="border: 1px solid black; display: inline-block; width: 40px; height: 20px;"></span> — rat
<i>Murine typhus (Rickettsia typhi)</i> —endemic typhus, Tabardillo in Mexico, Maxy's disease in United States, Manchurian typhus Vectors: <i>Xenopsylla cheopis</i> , <i>Pediculus humanus</i> ( <i>Liponyssus bacoti</i> ), <i>Polyp-          lax spinulosus</i> Coproctic transmission	

## D. Propagative multiplication and ovarian transfer in vector

Subgroup 7	host — tick — tick — man
	Laboratory: mouse — man
<i>Louping ill</i> (virus) Vector: <i>Ixodes ricinus</i> <i>Russian spring-summer encephalitis</i> Vectors—reservoir?: <i>Ixodes persulcatus</i> , <i>Dermacentor silvarum</i> , <i>Haemaphys-          alis concinna</i> Hosts: Rodents, birds	

Subgroup 8	tick — tick — rodent — tick — man
	and rodent — man
<i>Relapsing fever in United States (Borrelia turicatae, B. hermsi, B. parkeri)</i> Vectors: <i>Ornithodoros turicata</i> in Texas and Kansas, <i>O. hermsi</i> in California, <i>O. parkeri</i> in Wyoming, Montana and California, <i>O. talaje</i> in Arizona Hosts: Chipmunks, golden mantle squirrels, ground squirrels <i>Relapsing fever in Africa, Spain and Central America (Borrelia duttoni, B. kochii,          B. berbera, B. persica, B. hispanica, B. venezuelensis)</i> Vectors: <i>Ornithodoros erraticus</i> , <i>O. moubata</i> , <i>O. pallipes</i> , <i>O. maroccanus</i> , <i>O.          venezuelensis</i>	

Subgroup 9	tick — tick — rodent
	and tick — rodent — fly — man and tick — man
	and rodent — man and rodent — water — man
<i>Tularemia (Bacterium tularense)</i> Vectors: <i>Dermacentor andersoni</i> , <i>Chrysops discalis</i> Hosts: Cotton-tail rabbits, hares, squirrels, coyotes, rats, other mammals, birds	

TABLE I—Continued

	<div> <div>tick</div> <div>—</div> <div>tick</div> <div>—</div> <div>rodent</div> <div>—</div> <div>tick</div> <div>—</div> <div>man</div> </div>
Subgroup 10	<p>(a) <i>Tick typhus (Rickettsia rickettsii)</i>—Rocky Mountain spotted fever            Vectors: Western spotted fever, <i>Dermacentor andersoni</i>            Eastern spotted fever, <i>Dermacentor variabilis</i>            Hosts: Rabbits, ground squirrels, other rodents, dogs  <i>Fièvre boutonneuse (Rickettsia conorii)</i>—Marseilles fever            Vector: <i>Rhipicephalus sanguineus</i>            Host: Dogs</p> <p><i>South African tick bite fever (Rickettsia sp.)</i>            Vectors: <i>Amblyomma hebraeum</i>, <i>Boophilus decoloratus</i>  <i>Kenya fever (Rickettsia?)</i>            Vector: <i>Rhipicephalus sanguineus</i>            Host: Unknown</p> <p><i>Sao Paulo typhus</i>—Brazilian spotted fever            Vectors: <i>Amblyomma cajennense</i>, <i>A. striatum</i>            Hosts: Opossums, rabbits, caviars, plain dogs  <i>North Queensland tick typhus (Rickettsia?)</i>  <i>Siberian tick typhus?</i>  <i>Indian tick typhus?</i></p>
Subgroup 11	<div> <div>rodent</div> <div>—</div> <div>mite</div> <div>—</div> <div>mite</div> <div>—</div> <div>man</div> </div> <p>(b) <i>Tsutsugamushi disease (Rickettsia tsutsugamushi)</i>—mite typhus, rural typhus, scrub typhus, mite fever of Japan, Malaya, Burma, Sumatra, New Guinea and adjacent islands            Hosts: <i>Microtus</i>, <i>Rattus</i> sp., <i>Hadromys</i>, <i>Bandicota</i>, <i>Tupaia</i>            Vectors: <i>Trombicula akamushi</i>, <i>T. deliensis</i></p>
Subgroup 12	<div> <div>mouse</div> <div>—</div> <div>mite</div> <div>—</div> <div>man</div> </div> <p>Probably transovarian in vector, not yet demonstrated</p> <p>(c) <i>Rickettsial pox in New York City (Rickettsia akarii)</i>            Vector: <i>Allodermanyssus sanguineus</i>            Host: <i>Mus musculus</i></p>

## E. Helminthic infections: Homeothermic and poikilothermic animals

Subgroup 13	<div> <div>animal</div> <div>—</div> <div>man</div> <div>—</div> <div>animal</div> <div>and</div> <div>animal</div> <div>—</div> <div>man</div> </div> <p><i>Tapeworms (Taenia saginata, T. solium)</i>  <i>Hydatid worms (Echinococcus granulosus)</i>  <i>Trichinosis (Trichinella spiralis)</i>: Hogs, bears, dogs  <i>Dog hookworm (Ancylostoma braziliense, A. caninum)</i></p>
Subgroup 14	<div> <div>man</div> <div>—</div> <div>arthropod</div> <div>—</div> <div>man</div> </div> <div> <div>and</div> <div>animal</div> <div>—</div> <div>arthropod</div> <div>—</div> <div>man</div> </div> <p>Developmental in vector, no multiplication  <i>Filariasis (Wuchereria)</i>: <i>Culex</i> sp., <i>Aedes scutellaris</i>, <i>Taeniorhynchus</i> sp.  <i>Onchocerciasis (Onchocerca volvulus)</i>: <i>Simulium damnosum</i>  <i>Loa worm (Loa loa)</i>: <i>Chrysops dimidiata</i>  <i>Guinea worm (Dracunculus medinensis)</i>: <i>Cyclops</i>  <i>Dog tapeworm (Dipylidium caninum)</i>: <i>Ctenocephalides canis</i>  <i>Rat tapeworm (Hymenolepis diminuta)</i>: <i>Xenopsylla cheopis</i></p>
Subgroup 15	<div> <div>man</div> <div>—</div> <div>snail</div> <div>—</div> <div>man</div> </div> <p><i>Schistosomiasis (Schistosoma japonicum, S. haematobium, S. mansoni)</i></p>

TABLE I—Continued

Subgroup 16	{	man	—	snail	—	fish	—	man	
		<i>Chinese liver fluke (Clonorchis sinensis)</i>							
Subgroup 17	{	man	—	snail	—	arthropod (crab)	—	man	
		<i>Lung fluke (Paragonimus westermani)</i>							
Subgroup 18	{	man	—	snail	(vegetation)			man	
		<i>Large intestinal fluke (Fasciolopsis buskii)</i>							
Subgroup 19	{	sheep	—	snail	(vegetation)			man	
		<i>Sheep liver fluke (Fasciolopsis hepatica)</i>							
Subgroup 20	{	man or dog or cat	—	copepod	—			frog or fish	
		(Sparganum) man							
		<i>Broad fish tapeworm (Diphyllobothrium latum)</i>							
		<i>Mason's tapeworm (Diphyllobothrium mansonii)</i>							

citizens depend upon the breeding and raising of farm animals as their means of livelihood. These citizens are profoundly affected by the toll of animals taken by disease. Human health is greatly influenced by such foods as meat, milk, butter and cheese. These foods are relatively expensive since a considerable part of the cost is related to disease losses. It has been estimated that the annual cost of these losses exceeds one billion dollars. Huddleson (1947) estimated that brucellosis in one year deprived the milk-consuming public of 222,804,000 pounds of market milk. Equally significant are the data on the losses of calves. In Michigan alone in only a year, 108,000 infected cows of breeding age lost 16,240 calves; hence, 1,299,200 pounds of veal failed to reach the consumer. Further proof that brucellosis is a great destroyer of potentially available meat is furnished by the staggering fact that on hog-raising farms 82 per cent of the expected pig crops may be lost. Whatever the losses may be in other groups, it is clear that disease entails a heavy economic burden upon agricultural industry and directly on the economy of the country. Some progress has been made through education of the farmer concerning the economic losses, but he remains unaware of the health hazards of having infected livestock on his premises. Data recently collected in Iowa and Indiana reflect the high incidence of infections associated with diseases of domesticated animals in this occupational group. In nearly every communicable disease, public health efforts have lowered morbidity and mortality. The only diseases in which a noteworthy record has not been achieved are those of animal origin. Every physician has a share in the economic and educational problems created by the diseases of domesticated animals.

(b) The majority of microorganisms or viruses responsible for the diseases are capable of infecting in nature a great many animal species and, under experimental conditions, a variety of zoologically unrelated hosts. Man only accidentally and rarely becomes part of an infection chain.

(c) With the exception of the poxes, foot-and-mouth disease and glanders, the infections of the mammals frequently are chronic, and exhibit an outstanding tendency to remain latent or subclinical. The apparently healthy, though infected animal—a carrier or shedder—bears an epidemiologic relationship with the single or group infections of man. Early acute, but mild and atypical stages of the animal disease may be equally dangerous.

(d) After the heterogenous infection chain is formed, it seldom continues as a homogenous one or becomes again heterogenous. Human-to-human infections are rare. Outside the usual host cycle, the restricted mode of transmission is in part responsible for this break. Infections with bovine tubercle bacilli were formerly considered closed processes, conveyed only from animal to man, but in view of observations by Griffith and Munroe (1944) and others, man-to-man infection is now admitted. Rabies virus has occasionally been demonstrated in the saliva of children (Duffy et al., 1947) but authentic human-to-human transmissions have not been reported. To be sure, there is reason to suspect that the direction of the usual heterogenous infection chain may be reversed—infection of tuberculosis-free cattle by dairy hands with open bovine pulmonary tuberculosis. With this exception and possibly others as yet unrecognized, the disease agents which may operate in heterogenous chains maintain the species through continuous passages through the animal host. When the course is diverted and man becomes the host, it is likely to end blindly. As far as has been ascertained, with the exception of bovine tuberculosis, infection does not result from the exposure of a susceptible animal to a diseased human being.

(e) The clinical and anatomical character of the disease in man is quite similar to that in the animals. A change in host apparently fails to alter the principal diagnostic signs, provided the portal of entry of the parasites is the same. Some authors have pointed out that the brucella infections present noteworthy exceptions. In man, they say, it manifests itself as a septic fever, while in cattle as a localized process in the udder or in the placenta. These differences may be only relative. Very little is known concerning the early clinical course of *Brucella abortus* infection in cattle. According to Thomsen, cattle and, according to van der Hoeden (1946), horses infected with the brucella organisms may have fever of the undulating type. Blood cultures are frequently positive. Comparative clinical studies of the diseases listed in the first group show that no significant changes take place in the disease when the parasite changes hosts.

(f) At least 75 diseases of domestic and wild animals are of potential public health significance. The control by eradication appears to be easy in some, is more difficult in others and when wild rodents, monkeys and

birds act as reservoirs it is impossible. By destroying the infected animal, for example, the highly contagious foot-and-mouth disease has repeatedly been stamped out in the United States. Much faster progress has been made in the elimination of tuberculosis from cattle than has been possible with the same disease in man, by slaughtering the infected animal. Diminution of dense rodent and flea populations close to human settlements with newer rodenticides and insecticides may eliminate endemic typhus and plague. Whenever the principle of destroying the animal host is impractical and too costly, in some diseases regular immunization of exposed livestock may prove effective. Large-scale vaccination has reduced the number of outbreaks of anthrax in rural areas and with it the problem of human infections. It is earnestly hoped that the same may follow the use of calftuberculin vaccination against brucellosis. However, in the face of vast reservoirs of disease such as yellow fever in the wild regions of Africa and South America, or of sylvatic plague on nearly every continent, the hope of wiping them out becomes untenable. Measures directed against the arthropod vector and the use of protective vaccines for the exposed human population give, in the light of wartime experiences, some assurance that serious epidemics may be averted.

#### DIAGNOSIS AND TREATMENT OF DISEASES OF ANIMALS TRANSMISSIBLE TO MAN

It would, no doubt, be profitable and most gratifying to review the entire group of the diseases listed, but since the time is limited a selection has been made of a few infections which have attracted attention in recent years. Since the majority of practicing physicians rarely encounter these infections, the problem of diagnosis deserves special consideration. Although the diagnosis follows the pattern set for all infectious diseases, certain points deserve emphasis. A good epidemiological history may be most useful. This presupposes more than perfunctory knowledge of the mode of transmission. Experience has taught that the "prepared mind" is essential in spotting the accidental transmissions from animal to man. If a patient contracts a respiratory infection characterized by cough, fever, muscle aches and headaches, the following diagnostic possibilities should be considered: influenza, atypical pneumonia and psittacosis. In influenza the only disease source is another human being, and the incubation time is short. In contrast, atypical pneumonia has a longer incubation time—10 days to 3 weeks. Patients' association with birds, not merely psittacine varieties, suggests that the infection is psittacosis. Unfortunately, neither history nor physical examination makes it possible to recognize the nature of the infective agent. However, laboratory tests, which identify the specific etiologic factors, or serologic examinations, which indirectly indicate the nature of the infection, are available for diagnosis of the most important animal diseases transmissible to man. Promptness in diagnosis assures early efficient treatment.

Fortunately, with the advent of sulfonamide drugs and antibiotics, treatment of many of these infections has been effectively and dramatically improved. It will be the aim of the presentation which follows to emphasize some diagnostic and therapeutic aspects of the selected diseases.

*Salmonella Infections:* Human infection with salmonella is widespread, and the majority of outbreaks of food poisoning and endemic enteritis due to this group of organisms follow the consumption of food directly or indirectly associated with infection of some animal. In the United States poultry and other birds cause many cases. Barnes said that he considered the domestic fowl "the main animal reservoir of organisms affecting man." American spray-dried eggs during the war caused outbreaks of food poisoning in various places. On the other hand, the brilliant epidemiological studies by Watt in the Rio Grande Valley incriminate with equal force dogs, cats and ducks. Over 2 per cent of each of these animals were proved to harbor many varieties of salmonella in that locality. Some investigators found turkeys to harbor 23 types of salmonella (Pomeroy and Fenstermacher); turkey eggs from 8 per cent of the birds examined harbored the *Salmonella pullorum*. Market pork examined in Lexington, Kentucky, yielded salmonella (8 varieties) in 10 of 170 samples. One of 40 samples of beef was infected with *Salmonella seftenberg* (Cherry et al.). In spite of this widespread incidence of infection in domestic animals and their products used for food, the apparent infrequency of salmonella food poisoning requires some explanation. Human volunteer experiments by Hormaeche, Peluffo and Aleppo demonstrated that adults might ingest as many as 4,000,000,000 organisms without suffering from any symptoms at all, or from any other than mild afebrile diarrhea. Infants and old persons, however, appear to be considerably more susceptible than those in the middle group, and fatalities are restricted to these two age groups. In typhoid, cholera and dysentery, minute amounts of infective material may suffice to cause disease, but in food poisoning, large doses are generally necessary (Savage). The bacteriological diagnosis by means of modern selective culture media, as a rule, offers no difficulties, provided examinations of stool specimens obtained with rectal swabs are made repeatedly. Identification of the salmonella type has shown that *Salmonella typhi murium* is more often responsible for food poisoning than any other type. There is no specific treatment and the eradication of the animal reservoirs may offer insurmountable difficulties. Thorough systems of food inspection, refrigeration, pasteurization or cooking, which may succeed in reducing the number of the organisms, may be used as precautionary measures.

listed in *rax*: Anthrax, once an industrial hygienic problem because infected disease products were taken into tanneries, wool mills, glue factories, feed

(f) *Atis* (infected bone meal) and such places, is now a problem of public health. The statistics of Smyth show a steady increase in the occurrence in some, is natural anthrax during the 20 year period from 1919 to 1938,

but a definite decrease occurred during the five year period from 1939 to 1943. Wider application of preventive vaccination and other control measures during recent years is responsible for the improvement. The death rate for agricultural anthrax is higher than that for industrial anthrax and, unfortunately, continues to be high because diagnosis and treatment are delayed. Necessity for prompt recognition of human infections and efficient therapy with penicillin, which is more readily available than anthrax serum, places the problem of anthrax in the hands of the medical practitioner.

*Plague:* As a cause of death, plague plays a very subordinate rôle in the United States; during the past 15 years only 20 human cases have been definitely recognized, despite the fully established fact that plague is enzoötic in the wild rodent population over at least 14 Western states of the Union and in one province in Canada. Presence of this form of plague, now described as sylvatic plague, was suspected in 1903 and then definitely proved in 1908 in California. The official records for the period 1900 to 1947 attribute 48 cases of bubonic and 13 of pneumonic plague to the distribution of the rodent disease. Since 1935 human plague, most likely due to some contact with wild rodents, has been seen in Idaho (1 case), Nevada (1 case), Oregon (1 case) and Utah (2 cases). The question is constantly raised: What are the potential dangers of the sylvatic plague reservoirs? No definite answer has as yet been given. Disconcerting is the fact that during the past 15 years the few cases of human plague which have been recognized and reported have frequently served as sentinels to announce the dynamic activity of the primary rodent disease in areas where it had not previously been known to exist. The death of a sheep herder led to the demonstration of marmot plague in Oregon. A case of bubonic plague in southwest Utah, one in Idaho and others in San Bernardino, Placer and Siskiyou Counties in California, as well as in Douglas County, Nevada, were connected with previously unrecognized sylvatic plague pockets. Epizootics of wild rodent plague in which the fields and canyons are littered with carcasses of dead squirrels and the entrances to their burrows swarm with infected fleas rarely produce human infections. Why the disease fails to develop in man under such circumstances remains an unsolved mystery. Some unknown inherent weakness in the linkage formed by the flea must be responsible for the extreme infrequency of human infection in the open country. Domestic premises in rural communities, and cottages and cabins in summer resorts are the places where the infection most frequently has been contracted. The participation of mice and their ectoparasites in the exchange of the plague bacillus must be constantly kept in mind. A fatal bubonic plague infection in a boy residing in Siskiyou County was, in all probability, contracted in a barn where field mice exchanged their ectoparasites with those traceable to infected squirrels living in the adjacent fields and forest. On the other hand, direct contact in skinning or handling squirrels, bite wounds sustained through handling rodents or predators and



picking magpie nests have been associated with infections. The sporadicity of the outbreaks of bubonic plague in sections of the country, where it has never been identified and is seldom seen, makes it understandable why the diagnosis of human plague is so frequently missed during its course, and is made only after recovery or death. In my experience during the past 10 years in at least 14 of the 20 cases reported, mistaken diagnoses had been made before plague was recognized. At least in the West, every physician practicing in rural areas where squirrels are likely to be decimated by epizootics should constantly keep in mind that a painful edematous axillary or inguinal enlargement of the lymph node may be caused by plague. He should likewise remember that surgical treatment interferes with the local defense mechanism and is only too often followed by septicemia. Finally, early diagnosis is of greatest importance, not only to the patient whose recovery may depend on the early administration of streptomycin or sulfadiazine, but also to his family, physician and community. In case plague-pneumonia, secondary to the bubonic form, goes unrecognized an enormous number of highly virulent plague bacilli may be disseminated through the sputum and within a few days the infection chain may involve scores of victims. The outbreak of pneumonic plague in Oakland and Los Angeles are excellent examples of what will happen when bubonic plague is surgically treated, or when infectious plague pneumonia is diagnosed as double lobar pneumonia. By infrequent use of the bubo in its earliest stage with an 18 gauge needle, a small amount of edematous fluid may be aspirated readily and used for microscopic examination. The plague bacillus derived from these lesions has a characteristic morphologic appearance: round, ovoid or short safety-pin-shaped rods, marked by bipolar staining. With streptomycin now available as an outstanding specific therapeutic agent, the high case fatality rate of from 50 to 100 per cent for bubonic, carbuncular and pneumonic plague may be reduced to less than 5 per cent. Without delay, treatment consisting of intramuscular injection of 0.5 gm. every 6 hours for five to eight days or oral administration of sulfadiazine in doses adequate to create concentrations in the blood of from 10 to 15 mg. per 100 c.c. should be instituted.

Whatever disagreement may exist regarding the magnitude of the menace of sylvatic plague, it is imperative to protect rural communities against exposure. The maintenance of so-called rodent-free belts around towns is imperative. Control of dense rodent and flea populations close to human settlements with the newer rodenticides and DDT demands constant follow-up in order to be effective. Ecologic study of sylvatic plague may lead to the discovery of the type of hindrance which will in time liberate rural communities from a hazard which unfortunately is unrecognizable and immeasurable.

*Pasteurelloses:* Human infections with *Pasteurella multocida* are being more frequently recognized (Levy-Bruhl; Weber; Schipper). In 55 cases (five deaths), not always proved according to modern methods of bacteri-

ology to be cases of pasteurellosis, the infection was *local* with and without generalized symptoms. In almost half, animal bites were precursors of infection: it was proved that at least 21 of the infected persons were bitten by cats, four by dogs, one by a rabbit and one by a panther. Exposure to infected bovine animals, pigs or rabbit carcasses (muscle particularly) or consumption of infected rabbits brought on enteritis, conjunctivitis, appendicular abscesses and other manifestations. The generalized infections, symptoms of which vary widely from protracted, recurrent chills and fever to pneumonia and empyema (12 cases), meningitis (7) and puerperal sepsis, have been reported mainly from Europe. The sources of infection remained undetermined. Generalized infections frequently have proved fatal. Meningitis associated with *Pasteurella*, of which seven cases have been recorded, is usually sequel to skull fracture or sinusitis. It is not unlikely that the offending organism which induces meningitis subsequent to skull fracture comes from the nasal passages. Topley and Wilson observed the persistent carrying of a *Pasteurella* in the nose of an animal caretaker. Particularly interesting is the fact that *Pasteurella multocida* apparently may lie dormant in the tissues for months and only after trauma of subacutely infected tissues give rise to acute infection. Localized human *Pasteurella* infections, which may produce only phlegmon and abscess, are only too frequently complicated by osteomyelitis (Hansmann and Tully). It was epidemiologically proved that at one time in the City of Munich, where many cat bite wounds had been noted (Weber), 75 per cent of the cats harbored *Pasteurella* organisms in their nasal passages. *Pasteurella* obtained from the throats of animals have proved sensitive to 0.2 unit of penicillin per milliliter or less (Schipper).

*Pseudotuberculosis*: Dujardin-Beaumetz, Ballet and Cébron (1938) listed eight infections in man, all beyond question pseudotuberculosis, with the following geographic distribution: one in Japan, three in Hamburg, Germany, two in Czechoslovakia and two in Austria. All terminated fatally. These authors also mentioned the case reported by Albrecht in which the resected appendix of a 15 year old child, who had intimate contact with a cat, was proved by guinea pig inoculations to contain *Pasteurella pseudotuberculosis*. They also reported a case of fatal infection observed in France. To this list of 10 must be added three cases reported and one unreported in the United States (Topping et al.; Moss and Battle; Snyder and Vogel; Mason and Meyer) and one of mixed plague-pseudotuberculosis infection recorded by Macchiavello in Brazil. The descriptions of the 14 cases indicate that vague prodromal malaise was followed by abrupt febrile onset with headache, chills, general pains and occasional catarrhal symptoms. The fever was irregular or "septic," the temperature at times reaching 105° F. Anorexia, abdominal tenderness, constipation and variable degrees of leukocytosis usually were noted. Within a few days after onset the liver, and sometimes the spleen as well, became palpable and tender. Death was usually preceded by icterus, toxemia and stupor. In 11 cases the infection terminated fatally

between 10 and 18 days after symptoms were evidenced; in one, early in the third month. Diagnosis was established early by means of blood cultures and later by serum agglutination tests. Still other manifestations were septicemia, effusions into serous cavities, bronchitis, pulmonary engorgement and edema and parenchymatous changes in the liver, kidneys and myocardium. At autopsy pathognomonic caseous necrotic foci, 1 to 10 mm. in diameter, were scattered throughout the enlarged liver, spleen, mesenteric lymph nodes and occasionally in the pancreas. Hemochromatosis was frequently noted. In some cases ulcers had formed in the small intestines and colon. With the exception in the cases described by Macchiavello, all infections were abdominal, a fact which supports the contention that they were acquired via the digestive tract. In two cases the patients were known to have had contact with cats or garden soil contaminated with their excreta, while another patient had eaten rabbits.

According to recent tests, streptomycin (6 to 12 micrograms per cubic centimeter) inhibits rodent strains of pseudotuberculosis and hence should be useful in the treatment of these infections.

*Rabies:* That rabies as a prevalent animal disease is a problem in some communities is evidenced by the continuing demand for information and advice concerning postinfectious treatment with vaccine, as well as planning of effective rabies control programs. The knowledge that rabies is invariably fatal once it has developed makes it one of the most feared and notorious of diseases. The physician is usually confronted by the problem of estimating the possibility of infection in the bite victim; he must at the same time decide on the necessity for prophylactic treatment: two difficult decisions. Rhodes (1946) in a critical analysis of the value of human antirabies treatment emphasized a number of significant facts, among them that the mortality from rabies in untreated persons bitten by rabid animals is on the average no more than 15 per cent, and may well be less. Doubtless, in the past a considerable number of persons must have been treated with vaccines of very low immunizing potency. Furthermore, persons have doubtless been treated with antirabies vaccines who were not at risk from rabies. Though he concluded that many variable factors make any accurate appraisal of antirabies treatment in man impossible, he did suggest that on the evidence at present available, it is justifiable to continue to regard antirabies treatment as being of some value in the prevention of rabies, although it may not necessarily act by the orthodox process of active immunization. There is no justification for withholding treatment from persons thought to be at risk. The treatment as at present employed could probably be considerably improved, partly by the more frequent use of immune serum, and partly by the increased use of more potent vaccines. The vaccines found to be most effective in animal experiments are not yet generally used in human treatment. It is well known that in rare instances administration of rabies vaccine has resulted in neuromuscular accidents. In recent years, postpas-

teurian myelitis has been encountered more frequently. Consequently, a justified reluctance to administer postinfectious vaccination as an appeasement of one's conscience has developed. A concerted effort should, therefore, be made to control and possibly eradicate rabies. On a nationwide basis, the three major steps, (1) control of stray dogs, (2) vaccination of all dogs and (3) reduction of wild animal population when it is the reservoir, must be taken. The control of rabies is largely dependent on public interest and coöperation. An organized program of vaccination requires the fullest support of the medical profession and in particular the family physician whose advice to the owner of a dog is invaluable. Vaccination of dogs has proved its worth during the past few years. A single injection will protect 90 per cent of the dogs for one year, while three injections offer almost 100 per cent protection. On a voluntary basis, a program of canine vaccination in Massachusetts has freed that area from the disease for the first time since its introduction there in the eighteenth century. Alabama's experience with the vaccination program was similarly gratifying.

*Rickettsial Diseases:* The rickettsial diseases constitute an important and extremely interesting group of infections conveyed by arthropod vectors. There are five main categories listed under subgroups 3, 6, 10, 11 and 12. The first group, predominantly louse-borne, includes classical European endemic and epidemic typhus, the widespread flea-borne murine typhus of the Southern, Southeastern and Western United States (Beck and Van Allen). Mexican tabardillo and similar diseases in every part of the world belong in the second group. The third or spotted fever group contains the tick-borne diseases—both western and eastern Rocky Mountain spotted fever, Sao Paulo typhus, fièvre boutonneuse of the Mediterranean, South African and Kenya tick fever and others. The fourth group, borne by mites, includes scrub typhus, rural typhus of Malaya and rickettsial pox recently observed in the heart of New York. The fifth group—the Australian Q disease, nine-mile fever of Montana and Q fever of the Mediterranean, Greece, and the quite recently recognized infections on the American continent—probably constitutes a special category.

Rickettsiae are visible by ordinary microscopic examination and resemble bacteria in shape, but they are much smaller than influenza bacilli. Their growth requirements are only fulfilled by an obligate intracellular habitat. It has not been possible to grow them in the absence of living or at least surviving cells as, for example, the yolk sac of the embryonated chicken egg. In the invertebrate host they invade the cells of the intestinal tube and multiply within. Some arthropod hosts suffer by their presence; others do not. When transferred to man from the arthropod hosts, they cause disease with characteristic lesions. Since rickettsiae parasitize primarily the cells of the blood vessels, they give rise to vasculitis in the arterioles which leads to thrombosis and eventually necrosis. Perivascular infiltration by mononuclears, plasma cells and polymorphonuclear elements produces tubercular

nodules in the organs and tissues. These changes take place in the skin and cause the characteristic rash in the mucous and serous membranes and hemorrhages in various organs and in the central nervous system. The participation of the neuroglia cells in the reaction gives rise to the mental symptoms. The illness resulting is clinically characterized by an incubation period of one to three weeks, by sudden onset of headache and muscular pains and by fever lasting up to three weeks and usually ending by rapid lysis or crisis. In severe cases, a characteristic rash appears on about the fifth day after the other symptoms are manifest. Sera agglutinate certain strains of proteus (Weil-Felix reaction) and give complement-fixation reactions with specific antigens prepared from the respective strains of rickettsiae. The location of the maculopapular rash, first on the wrist or ankles, suggests tick-borne spotted fever, while a roseola rash on the trunk is diagnostically indicative of typhus. The clinical pathology of the rickettsial disease is very interesting; in all severe cases hypoproteinemia, drop in the concentration of plasma chlorides and increase in that of nonprotein nitrogen accompany the dehydration. Correction of these disturbances should be attempted by means of an adequate fluid intake and blood plasma transfusions. Many efforts have been made to find a substance of therapeutic value in rickettsial disease. After early trials with para-aminobenzoic acid made by the United States of America Typhus Commission Unit in Cairo, Egypt, the conclusion was reached that large doses exert a definite beneficial effect in the course of louse-borne typhus if treatment is started in the first week of illness. The drug, which has also been used at other centers, has been given by mouth; initial doses varied from 4 to 8 gm. and subsequent doses of 2 gm. were administered every two hours. Concentrations of from 10 to 20 mg. per 100 c.c. were maintained until the illness subsided (Snyder et al.). Since its effectiveness was demonstrated in louse-borne typhus, PABA in form of the sodium salt or in other conveniently administered forms has been successfully used in the treatment of endemic typhus (Smith and others), Rocky Mountain spotted fever (Greeley) and scrub typhus (Tierney). Curative action of the pure chemical due to its low toxicity has been excellent, provided therapy is begun early and blood concentrations of from 10 to 20 mg. for typhus and 35 to 40 mg. per 100 c.c. for Rocky Mountain spotted fever are maintained throughout the entire course of therapy. Leukocyte counts should be made daily; if the cell count falls below 3,000 serious consideration should be given to termination of therapy. The urine must be kept slightly alkaline to prevent the formation of crystals in the renal tubules. Preliminary experiments on embryonated eggs and on mice infected with the rickettsial agents of scrub typhus, epidemic and endemic typhus, Rocky Mountain spotted fever and rickettsial pox revealed that the new antibiotic, chloromycetin, has a remarkable therapeutic effect on these infections. Its low toxicity, its absorption from the alimentary tract and its beneficial effect even late in the disease suggest that it may be valuable in the treatment of patients (Smadel and Jackson):

The preventive measures against these infections are directed chiefly toward (1) elimination of the reservoirs—insect and mammalian and (2) specific immunization. The extraordinary effectiveness of the chemical DDT in destroying lice on garments and bedding has made obsolete the elaborate measures of delousing used in the past. Elimination of rats and rat fleas through spraying of rat holes or burrows and rat runs with DDT reduces the incidence of endemic typhus. Utilization of specific chemically-killed yolk sac vaccines has greatly reduced the incidence, severity and mortality of many of the most important rickettsial diseases except scrub typhus.

*Q Fever:* Q fever, originally discovered and described as a rickettsial disease in Queensland, Australia, in 1935, has risen in status from an infection of localized interest to one of world-wide importance. While ticks infected with *Coxiella (Rickettsia) burneti* were found in many parts of the United States before 1946, only a few naturally occurring infections have been established here. During the war the infection was assuming considerable importance when it was discovered to exist endemically and epidemically in the Mediterranean area and sporadically in Panama. Since then it has been proved to exist in Switzerland and Germany. Two explosive outbreaks of Q fever, one with 55 cases in Amarillo, Texas, in March, 1946 (Topping et al.), and a second in the stockyards of Chicago (Shepard), all infections more or less closely associated with the handling of cattle, focused attention on the probable prevalence of the infection in the United States. The failure to detect more cases in the past may possibly have been due to the use of a weakly reactive strain of the *Coxiella burneti* as antigen in the serological tests. The epidemiologic studies in 1946 produced no evidence of transmission by ticks, and it was thought that infection may have been incurred by inhalation of dust containing material contaminated by the excreta of infected cattle. Furthermore, the clinical observations disclosed that the disease picture was extremely varied, ranging from sub-clinical attacks and mild influenza-like illness with little evidence of pulmonary involvement through severe atypical pneumonia and pneumonitis to fatality (two in Amarillo). Convalescent sera of patients gave complement-fixation reactions, which reached the maximal titer of 1:320 about the fourth or fifth week.

In the spring of 1947 Q fever was clinically and serologically proved in 17 cases in Los Angeles County. Subsequently, studies of over 150 additional cases indicated that this infection is endemic in southern California (Huebner et al., 1948). Proximity to dairies by reason of occupation or residence was a common factor in the histories of more than 50 per cent. Serological surveys on 2,010 cows in the Los Angeles County area disclosed that 266 or 13 per cent possessed serum antibodies against Q fever. Not less than 12 dairies were found to have cows with positive reactions in their herds. More recently, the infection rate established by serologic tests in a dairy in Ventura County was 15 per cent. Less than 2 per cent of the

calves and bulls tested yielded serum reactions indicative of Q fever. The absence of demonstrable illness in the reacting animal and the failure to recover the rickettsia from the whole blood and blood clots suggested some local infection. Since epidemiologic data pointed to the involvement of dairies in the cases observed shortly before in man, every effort was made to obtain information on the mode of spread of the disease. Pooled specimens of flies, mosquitoes and mites, and of urine and feces from infected cows were inoculated into guinea pigs. Completely negative results were obtained. Finally, raw milk from suspected dairies was tested. Of 151 attempts by inoculating guinea pigs with the secretion, the animals became infected in 63 instances and yielded from the spleen the rickettsial organism, which by all available criteria was identified as *Coxiella burneti*. To date the milk of at least 12 dairies has been proved to be infected. The relative ease with which *Coxiella burneti* is recovered and widely distributed in southern California from milk of dairies, together with the occurrence of Q fever in the human population in the same area, suggests a causal relationship. Whether or not milk represents an effective source of infection to man, however, cannot be determined by the data thus far available. Quite recently three patients with clinical symptoms of undulant fever and a history of heavy consumption of raw milk, although serologically negative for *Brucella abortus*, furnished blood sera in which specific antibodies against Q fever were present in very high titer ( $> 1:640$ ). Although the evidence presented by outbreaks in packing houses, stockyards and laboratories incriminated the pulmonary route of infection, clinical and epidemiological data recently unearthed reveal some similarity to those which have collected concerning undulant fever. As soon as an adequate supply of strongly reactive antigens is obtainable, it is imperative that sera in all cases in which brucellosis is suspected be tested for Q fever antibodies. Extensive studies now in progress in California will doubtless help to clarify the problem of Q fever. In this connection, it may be mentioned that an incomplete serological survey by Shepard showed Q fever antibodies had been produced in cows in many Western states. Preliminary investigations lend encouragement that the spread of the infection may be at least partially checked. Pasteurization, by the flash method at 160° F., apparently destroys the *Coxiella burneti*. Furthermore, immunological protection may be given to exposed workers in laboratories, slaughterhouses and dairies by means of recently developed yolk sac formalinized vaccines prepared by methods similar to those used in the commercial manufacture of epidemic typhus vaccine. These antigens in single-dose injections elicit specific complement-fixing antibodies in human beings. No opportunity has been afforded to obtain information on the resistance of those vaccinated to infection with Q fever (Smadel et al., 1948). Nothing is known concerning the mode of infection and pathogenesis of *Coxiella burneti* infection in cattle. Consequently, plans for the control must be deferred until this information is available.

In man's environment, then, there exists a complex host-parasite relationship between animals and various infective organisms. Because the effects of human entrance into the infection chain, as suggested throughout this review, are in many instances undesirable and because the means of avoiding it are as yet known in too few instances, efforts must be continued to increase knowledge of preventing, recognizing and treating these accidental infections. Meanwhile, it is important that all available information be effectively used.

## BIBLIOGRAPHY

- BARNES, L. A.: Pathogenic enteric bacilli. II. The salmonella group, U. S. Nav. Med. Bull., 1944, xliii, 939-949.
- BECK, M. D., and VAN ALLEN, A.: Typhus fever in California 1916-1945 inclusive. An epidemiologic and field laboratory study, Am. Jr. Hyg., 1947, xlv, 335-354.
- CHERRY, W. B., SCHERAGO, M., and WEAVER, R. H.: The occurrence of *Salmonella* in retail meat products, Am. Jr. Hyg., 1943, xxxvii, 211-215.
- DUFFY, C. E., WOOLEY, P. V. JR., and NOLTING, W. S.: Rabies. A case report with notes on the isolation of the virus from saliva, Jr. Pediat., 1947, xxxi, 440-447.
- DUJARDIN-BEAUMETZ, E., BALLEZ, B., and CÉBRON, J.: La pseudo-tuberculose chez l'homme, Presse méd., 1938, xlv, 43-45; Rev. de path. comparée, 1938, xxxviii, 884-893.
- GREELEY, D. McL.: The treatment and prevention of Rocky Mountain spotted fever in children, Med. Clin. North Am., 1947, xxxi, 647-658.
- GRIFFITH, A. S., and MUNROE, W. T.: Human pulmonary tuberculosis of bovine origin in Great Britain, Jr. Hyg., 1944, xliii, 229-240.
- HANSMANN, G. H., and TULLY, M.: Cat-bite and scratch wounds with consequent Pasteurella infection of man, Am. Jr. Clin. Path., 1945, xv, 312-318.
- VAN DER HOEDEN, J.: De zoönosen. Infectieziekten der dieren die op den mensch kunnen overgaan en de ziekten die daardoor bij dezen worden teweeggebracht, 1946, H. E. Stenfert Kroese's Uitgevers-Mij N. V., Leiden, 444 pp.
- HORMAECHÉ, ESTENIO, PELUFFO, C. A., and ALEPPO, P. L.: Nueva contribución al estudio etiológico de las "diarreas infantiles de verrano." Las "Salmonelas" en las enterocolitis de la infancia, Arch. urug. de med., cir. y especialid., 1936, ix, 113-162.
- HUDDLESON, I. F.: The relation of brucellosis to human welfare, Ann. New York Acad. Sci., 1947, xcvi, 415-428.
- HUEBNER, R. J., JELLISON, W. L., BECK, M. D., PARKER, R. R., and SHEPARD, C. C.: Q fever studies in southern California. I. Recovery of *Rickettsia burneti* from raw milk, Pub. Health Rep., 1948, lxiii, 214-222.
- LEVY-BRUHL, M.: Les pasteurelloses humaines, Ann. de méd., 1938, xlv, 406-437.
- MACCHIAVELLO, A.: Contribuciones al estudio de la peste bubónica en el nordeste del Brasil, Oficina Sanitaria Panamericana Publicación No. 165, 243-277.
- MASON, D. G., and MEYER, K. F.: Unpublished data.
- MOSS, E. S., and BATTLE, J. D., JR.: Human infection with *Pasteurella pseudo-tuberculosis rodentium* of Pfeiffer; report of a case, Am. Jr. Clin. Path., 1941, xi, 677-699.
- POMEROY, B. S., and FENSTERMACHER, R.: Salmonella infection in turkeys, Am. Jr. Vet. Res., 1944, v, 282-288.
- RHODES, A. J.: Anti-rabies treatment. A discussion of its value in the light of recent experimental work, Trop. Dis. Bull., 1946, xliii, 987-991.
- SAVAGE, WILLIAM: Paratyphoid fever: an epidemiological study, Jr. Hyg., 1942, xlii, 393-410.
- SCHIPPER, G. J.: Unusual pathogenicity of *Pasteurella multocida* isolated from the throats of common wild rats, Bull. Johns Hopkins Hosp., 1947, lxxxix, 333-356.



- SHEPARD, C. C.: Paper read before the American Society of Tropical Medicine, Atlanta, 1947.
- SHEPARD, C. C.: An outbreak of Q fever in a Chicago packing house, *Am. Jr. Hyg.*, 1947, xlv, 185-192.
- SMADEL, J. E., and JACKSON, E. B.: Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections, *Science*, 1947, cvi, 418-419.
- SMADEL, J. E., SNYDER, M. J., and ROBBINS, F. C.: Vaccination against Q fever, *Am. Jr. Hyg.*, 1948, xlvii, 71-81.
- SMITH, P. K.: The use of para-aminobenzoic acid in endemic (murine) typhus, *Jr. Am. Med. Assoc.*, 1946, cxxx, 1114-1117.
- SMYTH, H. T.: Industrial anthrax in the United States, 1939-1943, *Am. Jr. Pub. Health*, 1945, xxxv, 850-858.
- SNYDER, G. A. C., and VOGEL, N. J.: Human infection by *Pasteurella pseudotuberculosis*; report of case with recovery, *Northwest Med.*, 1943, xlii, 14-15.
- SNYDER, J. C., YOEMANS, A., CLEMENT, D. H., MURRAY, E. S., ZARAFONETIS, C. J. D., and TIERNEY, N. A.: Further observations on the treatment of typhus fever with para-aminobenzoic acid, *Ann. Int. Med.*, 1947, xxvii, 1-27.
- TIERNEY, N. A.: Effect of para-aminobenzoic acid in tsutsugamushi disease, *Jr. Am. Med. Assoc.*, 1946, cxxx, 280-285.
- TOPLEY and WILSON's principles of bacteriology and immunity (revised by G. S. Wilson and A. A. Miles), 3rd Edition, 1946, Williams & Wilkins, Baltimore, vol. 2, p. 1648.
- TOPPING, N. H., SHEPARD, C. C., and IRONS, J. V.: Q fever in the United States. I. Epidemiologic studies on an outbreak among stock handlers and slaughterhouse workers, *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 813-815.
- TOPPING, N. H., WATTS, C. E., and LILLIE, R. D.: A case of human infection with *P. pseudotuberculosis rodentium*, *Pub. Health Rep.*, 1938, liii, 1340-1352.
- WATTS, JAMES: Personal communication to the author, 1948.
- WEBER, B.: Pasteurellosen beim Menschen nach Tierbissen, *Zentralbl. f. Chir.*, 1941, lxviii, 653-657.

# CASE REPORTS

---

## ACUTE IDIOPATHIC HYPOPROTHROMBINEMIA, RESPONSE TO MASSIVE DOSES OF VITAMIN K\*

By IRENA A. HEINDL,† M.D., BERNHARD G. ANDERSON,† M.D., and  
RICHARD DUFFICY FRIEDLANDER,‡ M.D., F.A.C.P.,  
*San Francisco, California*

IN 1941 Rhoads and Fitz-Hugh<sup>1</sup> described the first case of hypoprothrombinemia in which the previously accepted causes of vitamin K deficiency, i.e., liver damage and impaired intestinal absorption, seemed to play no major rôle. Thus, they established a new subgroup of the hemorrhagic disorders, namely, idiopathic hypoprothrombinemia. Since then, several similar cases<sup>2, 3, 4, 5, 6, 7, 8</sup> have been reported, differing somewhat from one another, but all with a prolonged prothrombin time. The present case report is added to the small group already in the literature because of the dramatic response to large doses of vitamin K.

### CASE REPORT

The patient, a 43 year old white, married housewife, was essentially well until July 1, 1947 when she first noticed the appearance of "black and blue spots" on the arms and legs. The size and number of these ecchymoses rapidly increased and on July 3, 1947, she began to bleed from the mouth and gums, associated with the sudden development of an extensive extravasation of blood into the soft tissues of the ventral surface of the tongue and the entire anterior part of the neck. The same evening, the patient noticed gross blood in the urine. Because of increasing respiratory distress and laryngeal stridor, she was admitted to the hospital shortly after midnight July 4, 1947.

The past history revealed no similar episodes, in fact, she had never noticed any tendency to bruise before. Her menstrual periods had been normal until four years previously when one ovary and part of the other had been removed because of cystic degeneration. Following this procedure menses occurred every one to three months, and were never excessive until her last period (beginning May 30, 1947) which lasted seven days and was quite profuse.

During the preceding eight years, the patient had been bothered intermittently by aching pain in the left upper thigh, a complaint for which she had seen many physicians. Numerous diagnostic surveys were carried out without attaining a satisfactory etiologic explanation and finally in 1945, the left femoral triangle was explored, no abnormalities being found. Routine hematologic studies at this time were within normal limits (table 1). During the four weeks prior to the present

\* Presented in brief before the Western Regional Meeting of the American Federation for Clinical Research, November 6, 1947, San Francisco, California.

† Members of the Resident Staff, Medical Service, Franklin Hospital, San Francisco, California.

‡ Associate Clinical Professor of Medicine, University of California Medical School, San Francisco, California.

hospital entry, her family physician had advised her to take empirin compound \* with one-half grain codeine three times daily for a recurrence of the pain in the left thigh. This medication was taken fairly regularly and was the only drug taken prior to the onset of her present illness.

The family history was negative for a hemorrhagic diathesis and the patient's 8 year old daughter had never shown any bleeding tendencies.

Physical examination showed a well developed and well nourished female of stated age in severe respiratory distress. Her respirations were 30 per minute, the tachypnea being associated with laryngeal stridor, the pulse rate 100 per minute and the blood pressure 130 mm. Hg systolic and 70 mm. diastolic. The skin was pale and cool, and over the extremities there were numerous ecchymotic areas. Extensive hemorrhage into the subcutaneous tissues of the neck anteriorly and laterally had produced marked swelling and discoloration giving the patient a "bull-neck" appearance. There was marginal oozing of the gums and a sublingual extravasation of blood about the size of a golf ball had forced the tongue back and upwards against the roof of the mouth and naso-pharynx causing considerable discomfort. This and the swelling in the neck were undoubtedly responsible for her respiratory difficulties, since the cardiac examination was negative and the lung fields were clear. The liver and spleen were not palpable and there were no abdominal masses or tenderness. A blood count performed shortly before she entered the hospital showed a hemoglobin

TABLE I

	1944 Sept. 26	1945 Feb. 8	1947 July 3	July 4	July 5	July 6	July 7
Hgb.	13.5 gm.	13.3 gm.	11.0 gm.	8.2 gm.	9.2 gm.	8.7 gm.	11.2 gm.
RBC	4.31 M	4.52 M	3.40 M	2.78 M	3.12 M	2.90 M	3.76 M
WBC	6750	8600	9250	19,600	—	11,400	12,400
PMN	41F 54 13NF	66F 77 11NF	79F 98 19NF	—	—	90	77
E	—	—	—	—	—	1	7
B	1	3	—	—	—	—	2
L	36	14	2	—	—	9	14
M	9	5	—	—	—	—	—
Prothrombin time	—	—	—	4 min. 25 sec. (control: 16.5 sec.)	1 min. 6 sec. (control: 17 sec.)	43 sec. (control: 15 sec.)	—
Platelets	—	—	200,000	243,000	—	—	—
Bleeding time	—	—	—	6 min.	—	—	—
Clotting time	—	—	—	13.5 min.	—	—	—
Clot retraction	—	—	—	Began in 3 hrs. Complete 24 hrs.	—	—	—
Blood chemistry	—	—	—	—	—	—	Plasma prot. 6.5 gm. N.P.N. 31 mg.
Icterus index	—	—	—	—	—	—	—
Transfusions whole blood	—	—	—	500 c.c.	500 c.c.	500 c.c.	—
Hykinone I.V.	—	—	—	280.4 mg.	72 mg.	72 mg.	72 mg.

\* Empirin compound contains aspirin  $3\frac{1}{2}$  grains, caffeine  $\frac{1}{2}$  grain and phenacetin  $2\frac{1}{2}$  grains.

TABLE I (Continued)

	July 8	July 9	July 10	July 11	Aug. 5	Oct. 18
Hgb.	—	13.8 gm.	14.7 gm.	—	13.8 gm.	14.3 gm.
RBC	—	4.2 M	4.47 M	—	4.16 M	4.15 M
WBC	—	—	6000	—	6950	9100
PMN	—	—	56	—	65	68
E	—	—	2	—	6	1
B	—	—	—	—	6	—
L	—	—	42	—	23	30
M	—	—	—	—	—	1
Prothrombin time	33 sec. (control: 15 sec.)	—	24 sec. (control: 16.5 sec.)	—	23.5 sec. (control: 20 sec.)	17 sec. (control: 18 sec.)
Platelets	—	—	291,000	—	246,000	251,000
Bleeding time	—	—	—	1 min.	2 min.	2 min.
Clotting time	—	—	—	5 min.	3½ min.	5 min.
Clot retraction	—	—	—	Began in 2 hrs. Complete 18 hrs.	Began in 30 min. Complete 4 hrs.	Began in 1 hr. Complete 4 hrs.
Blood chemistry	—	—	—	Album.: 3.63 gm.% Glob.: 2.08 gm.%	Album.: 4.22 gm.% Glob.: 3.11 gm.%	Plasma Prot. 6.21 gm.% Album.: 4.1 gm. Glob.: 2.1 gm.
Icterus index	—	—	—	5 units	7 units	5 units
Transfusions whole blood	500 c.c.	—	—	—	—	—
Hykinone I.V.	72 mg.	4.8 mg.	4.8 mg.	4.8 mg.	—	—

of 11 grams, the red blood cell count was 3.4 million, white blood cell count 9250, with 77 per cent neutrophils, 21 per cent lymphocytes, and 2 per cent monocytes. The platelet count was 200,000.

The immediate problem was the respiratory distress. Tracheotomy or laryngeal intubation was seriously considered.\* Because of the danger of further hemorrhage attendant upon the former procedure and the practical impossibility of the latter and the fact that despite the laryngeal stridor there seemed to be a fairly adequate airway, it was decided to place the patient in an oxygen tent. Following this and sedation with dilaudid, the patient soon became more comfortable and an intravenous infusion of 5 per cent glucose in 1000 c.c. of Ringer's solution containing 200 mg. of ascorbic acid and 4.8 mg. of Hykinone † was administered slowly. During the night she passed a large, soft, black stool which gave a positive guaiac test.

In the morning the patient seemed considerably improved and her breathing was easier except for mucous collections in the throat. This was relieved and seemed to be controlled by atropine sulfate 1/200 gr. p.r.n. After the completion of blood studies, another infusion of 5 per cent glucose in Ringer's solution was given with 200 mg. of ascorbic acid and 4.8 mg. of Hykinone. The hematologic examination now showed 8.2 grams of hemoglobin, red blood cells 2.78 million, white blood cells 19,600 with 98 per cent neutrophils, and 2 per cent lymphocytes. The platelet count

\* The authors are indebted to Dr. Lewis F. Morrison for his advice in the management of the case from this standpoint.

† Hykinone, menadione bisulfate, Abbott.

was 243,000; the prothrombin time (Quick's method) 4 minutes, 25 seconds (control 16.5 seconds). The clotting time (capillary tube method) was 13½ minutes, the bleeding time (Duke's method) 30 minutes. It was noted that blood was still oozing from the site of venipuncture performed eight hours before. A transfusion of 500 c.c. of whole citrated blood was given and large doses of Hykinone were then administered intravenously, 72 mg. every four hours until the prothrombin time was 1 minute, 6 seconds (control 17 seconds) 24 hours later. At that time, 280.4 mg. of the drug had been given intravenously.

On July 5, 1947 another transfusion of 500 c.c. of whole citrated blood was given and it was decided to give 72 mg. of Hykinone daily until the prothrombin time approximated the normal. Demerol in 100 mg. doses was given intramuscularly to control pain and restlessness.

On the following day, July 6, the patient expectorated a few dark red blood clots and passed some bloody urine. After this, there were no further bloody stools, urine or expectoration and there was no further evidence of fresh subcutaneous hemorrhages; in fact, she was definitely improving. The prothrombin time was now 43



FIG. 1. Appearance of patient four days after onset of illness (July 8, 1947).

seconds (control 15 seconds). Another transfusion was given, although it was possible for the patient to swallow small amounts of liquids and soft foods. Supplemental therapy included multivitamin tablets, ferrous gluconate and crude liver extract intramuscularly. On July 7, her temperature rose to 103° F. but since no evidence of infection could be found (blood culture negative), this was assumed to be due to the resorption of blood in the tissues. The plasma proteins on this date were 6.5 grams per 100 c.c. Although a possible azotemia was considered, the blood non-protein nitrogen was 31 mg. per cent. The blood Wassermann and Kahn tests were negative. The patient was now comfortable without the oxygen tent and on July 8, another transfusion was given although the prothrombin time was now 45 per cent of normal. The following day the red cell count was 4.2 million, and the hemoglobin was 13.8 grams. The dose of Hykinone was then reduced to 4.8 mg. daily and finally discontinued two days later when the prothrombin time was 24 seconds (control 16.5 seconds). By July 11, the patient was well enough to sit in a chair and on July 12, she was discharged from the hospital to convalesce at home. The total dose of Hykinone administered intravenously over a period of eight days was 585.6 milligrams.

While at home, the patient was advised to continue with oral multivitamin therapy and ferrous gluconate and was given intramuscular injections of crude liver extract intramuscularly twice weekly by her family physician. She received no further vitamin K therapy. She was seen again on October 18 at which time she reentered the hospital because of pain in the left hip region. Roentgen-ray studies showed calcification in the bursa overlying the greater trochanter of the left femur. The blood studies were repeated at this time and all were within normal limits (table 1). The prothrombin time was 17 seconds (control 18 seconds). Her symptoms were attributed to a chronic tendinitis of the left gluteus medius with calcification and secondary bursitis. This impression was confirmed at operation on October 28, 1947. It was felt that these findings were responsible for the symptomatology in the left hip region and thigh for the preceding eight years.

### DISCUSSION

The fulminating onset and dramatic recovery in this case have no parallel in the previously recorded cases of idiopathic hypoprothrombinemia. The only case which approached this one in rapidity has been described by Austin and Quastler,<sup>7</sup> but their patient had had periodic bleeding episodes over a period of several months and the autopsy findings showed widespread granulomatous lesions. These two cases are the only ones to which the term "acquired" might possibly be applied since, as may be seen in table 2, almost all of the other patients showed pathological bleeding tendencies early in life, lasting a few months to several years. All were males and were considered to have a congenital and/or hereditary background. Murphy and Clark,<sup>4</sup> Heinild<sup>5</sup> and Giordano<sup>3</sup> mention female siblings afflicted with bleeding tendencies but quote no complete studies.

The response to therapy was no less remarkable than the clinical picture on entry. We frankly did not expect the patient to survive and since the platelet count was normal and the prothrombin time had not yet been determined, the Hykinone and ascorbic acid were given empirically, yet the former none the less fortuitously in retrospect. Six hours after entry when the prothrombin time was found to be 4 minutes, 25 seconds (control 16.5 seconds) (after 4.2 mg. of Hykinone intravenously), it was decided to administer large doses of Hykinone intravenously without delay. Whether or not such tremendous doses were actually necessary is now a matter of speculation. It is quite possible that smaller amounts of the drug may have been as effective. Quick<sup>8</sup> and Fashena and Walker<sup>9</sup> described instances of low prothrombin concentrations, 8 per cent and 40 per cent respectively, responding to small doses of vitamin K, 30 mg. and 4 mg. Lucia<sup>20</sup> believes that in hypoprothrombinemia hemorrhagic phenomena only occur when the prothrombin concentration falls below 10 per cent. Aggeler et al.<sup>10</sup> report a case of hypoprothrombinemia due to exogenous dietary deficiency in which the prothrombin concentration (Quick) rose from 10 per cent to 55 per cent in 24 hours, after 5 mg. of synthetic vitamin K intravenously. However, the urgency of the situation and the relatively low toxicity of the drug seemed to justify our decision at the time. Only after the first 24 hours when oozing from the various sites of venipuncture had cleared and the prothrombin time was 1 minute, 6 seconds (control 17 seconds) did we feel safe in decreasing the dose of Hykinone. The rapid improvement in this case has been attributed primarily to Hykinone, yet the importance of the blood transfusions cannot be minimized.

TABLE II

Source	Age of Onset	Duration	Course	Sex	Family History	Prothrombin Evaluation	Coagulation Time	Clot Refraction	Bleeding Time	Tourniquet Test	Platelets	Fragility Test	Remarks
Rhoads and Fitz-Hugh, 1941	9 mos.	18 yrs.	Fatal	M	None	70 sec. to 120 sec. (Normal: 23 sec.) No response to vitamin K plus bile salts.	8-360 min.	Normal to poor	1-25 min.	Positive	140,000 to 416,000	—	Normal liver function tests. Calcium 9.8 to 10 mg.%. No excess antithrombin or antiprothrombin. Qualitative defect in fibrinogen. Autopsy revealed some atrophy of "liver columns" but inadequate to explain low prothrombin level.
Beard (Quoted by Quick), 1942	Birth	9 yrs.	Chronic	M	None	Prothrombin concentration 25% of normal. Intensive vitamin K therapy elevated it to 75%. Poor response to fresh whole blood transfusions.	Delayed	—	Not prolonged	—	Normal in number and quality	—	Original diagnosis—hemophilia.
Giordano, 1943	5 yrs.	17 yrs.	Chronic	M	Mother, father, brother, sister, with low prothrombin concentrations.	Prothrombin time (Quick) 210 sec. (normal 25 sec.) No response to vitamin K or parenteral liver extract. Plasma produced temporary rise to concentration 40% of normal.	4-6½ min.	Good	4-7½ min.	Positive	312,000	—	Liver function normal although serum proteins 5.4 gm.%. Low blood ascorbic acid (0.48 mg.%) which responded to cevitamic acid. Calcium 9 mg.%. Serum proteins low (5.34 to 5.9 gm.) in entire family.
Murphy and Clark, 1944	4 yrs.	14 yrs.	Chronic	M	Sister died at age of 4, "splenic anemia."	Prothrombin time (Quick) 60 sec. to 100 sec.—normal 16 sec. Resistant to vitamin K and bile salts. Bleeding temporarily controlled by whole blood only.	3-10 min. Normal	Good	1½-12 min.	Negative	113,600 to 358,000	Hemolysis began 0.45—ended 0.32.	Liver function tests normal; spleen slightly enlarged. Calcium 9.8 mg.%; blood ascorbic acid 1.5 mg.%. Fibrinogen (331 mg.%) normal but with qualitative defect. No excess antithrombin or antiprothrombin. Nail-bed capillaries abnormal as in pseudohemophilia.

TABLE II (Continued)

Source	Age of Onset	Duration	Course	Sex	Family History	Prothrombin Evaluation	Coagulation Time	Clot Refraction	Bleeding Time	Tourniquet Test	Platelets	Fragility Test	Remarks
Hefild, 1914 (a)	7 days	3½ yrs.	Chronic	M	Maternal aunt with hypoprothrombinemia. Uncle with bleeding tendency. Brother (see below).	Prolonged prothrombin time	—	—	—	—	73,000	—	Also fibrinopenia (0.14 gm. %); transitory thrombocytopenia.
(b)	7 days	2 yrs.	Chronic	M	Brother to above	Prothrombin time 120 sec. Normal 18-20 sec. (Larsen and Plum). Responded to transfusions.	—	—	—	—	20,000 to 159,000	—	Fibrinopenia (0.057 gm. %). Bone marrow rich in cells with considerable lymphocytosis and reduced erythropoiesis.
Hausner, 1915	14 days	5 yrs.	Chronic	M	Brother with prothrombin concentration—53%.	Prothrombin concentration 25% to 65% of normal. No response to vitamin K. Slight response to transfusions of whole blood.	3 min., 7 sec. to 11 min., 20 sec.	Good 20-60 min.	2 min. to 3 min.	Negative	238,000 to 716,000	—	Liver function tests normal. Calcium 11.6 mg. % Fibrinogen 0.34 gm. %. No increase in antithrombin.
Austin and Quastler, 1915	56 yrs.	10 mos.	Fatal	M	None	Prothrombin concentrations from 6% to 90% of normal. Resistant to vitamin K, bile salts and all other therapy.	—	Very	1 min., 15 sec. to 4 min.	Negative	198,000 to 277,000	Normal	Autopsy: Widespread granulomatous lesions, ? I.B., Hodgkin's sarcoma or sarcoïdosis. Moderate liver damage. No excess antithrombin or antiprothrombin. Fibrinogen, 0.63 gm. %. Calcium 9.4 mg. %.
Quick, 1916	Unknown	22 yrs.	Chronic	M	Mother and sister with prothrombin concentration around 50%.	Prothrombin concentration 35% to 50% of normal. No response to vitamin K.	—	—	—	—	—	—	Hypoprothrombinemia discovered accidentally; no history of pathologic bleeding. "Probably congenital and hereditary."



The seriousness of the patient's condition, however, would not have permitted an attempt at treatment with vitamin K alone. According to Aggeler,<sup>11</sup> one blood transfusion might possibly have raised the prothrombin concentration to 12 per cent, but rather certainly not to 25 per cent. The ascorbic acid obviously did not affect the prothrombin time. Even in dicumarol poisoning the use of large doses of Hykinone alone has not been considered a complete substitute for blood transfusions. In fact, the similarity between the clinical picture in this case and that seen following dicumarol overdosage strongly influenced our giving large doses of vitamin K. The marked improvement in this patient following Hykinone is in contrast to the lack of response to this drug in the majority of previously reported cases.

No satisfactory explanation for the hemorrhagic phenomena in this patient is offered. Her otherwise healthy appearance and total lack of gastrointestinal symptomatology would seem to rule out faulty absorption. It was felt that diffuse hepatic disease was not likely since the total plasma proteins, albumin-globulin ratio, icterus index and cephalin flocculation test were all within normal limits. As a matter of fact, in this particular case one might infer that the rapid rise in prothrombin concentration following the administrations of vitamin K was in itself evidence of hepatic function that could not have been too badly impaired.

The effect of salicylates on the blood prothrombin concentration obviously cannot be ignored since the patient had been taking empirin compound regularly over a period of several months, yet the daily dose of aspirin did not amount to more than 10 to 15 grains. Link et al.<sup>12</sup> found salicylic acid to be one of the end products in the breakdown of dicumarol and later showed that in rats on a low vitamin K diet, a single dose of salicylic acid induced temporary hypoprothrombinemia. Coombs et al.<sup>13</sup> in a series of 17 rheumatic fever patients and Butt et al.<sup>14</sup> in a similar series of 50 patients, all taking moderate to large doses of sodium salicylate (6 to 10 grams daily), reported a definite, but only moderate, drop in prothrombin time after administration of the drug for four days or more; a drop insufficient to cause spontaneous bleeding. Fashena and Walker<sup>9</sup> produced experimentally a prolongation of the prothrombin time on the second day of salicylate administration, but a spontaneous return to normal ensued in the face of continued medication. Similar results have been described by Meyer and Howard<sup>15</sup> and Rapoport, Wing and Guest.<sup>16</sup> Petechial hemorrhages due to thrombocytopenia attributable to salicylate administration have been reported,<sup>17, 18</sup> as well as frank purpura,<sup>18, 19</sup> but no blood studies were carried out in the latter instances. Ashworth and McKemie<sup>20</sup> have attributed two deaths to salicylate poisoning. These cases showed very extensive petechial hemorrhages at autopsy, which the authors concluded were due to capillary damage and hypoprothrombinemia but no antemortem hematologic studies had been carried out.

It would appear from the current literature that salicylates may definitely lower the prothrombin concentration, but we have seen no report, either clinical or experimental in which salicylates produced a hypoprothrombinemia associated with almost fatal hemorrhagic phenomena. If salicylates are to be held accountable in this case, it must be assumed that the patient suddenly developed an idiosyncrasy to the drug, not unlike anaphylaxis, in which the ability of the liver to synthesize prothrombin was seriously impaired.

## SUMMARY

1. A case of so-called idiopathic hypoprothrombinemia successfully treated with large doses of vitamin K is described.
2. The influence of salicylates on prothrombin time is discussed.
3. Previously reported cases of idiopathic hypoprothrombinemia and their points of difference with this case are discussed.

## BIBLIOGRAPHY

1. RHOADS, J. E., and FITZ-HUGH, T., JR.: Idiopathic hypoprothrombinemia—an apparently unrecorded condition, *Am. Jr. Med. Sci.*, 1941, ccii, 662.
2. QUICK, A. J.: The hemorrhagic diseases and the physiology of hemostasis, 1942, C. C. Thomas, Springfield.
3. GIORDANO, A. S.: Idiopathic hypoprothrombinemia, *Am. Jr. Clin. Path.*, 1943, xiii, 285.
4. MURPHY, F. D., and CLARK, J. M.: Idiopathic hypoprothrombinemia, *Am. Jr. Med. Sci.*, 1944, ccvii, 77.
5. HEINILD, S.: On familial constitutional fibrinopenia—some observations with regard to the simultaneous appearance of fibrinopenia, thrombopenia, and hypoprothrombinemia, *Acta med. Scandinav.*, 1944, cxviii, 479.
6. HAUSER, F.: Familial, vitamin-K resistant hypoprothrombinemia, *Ann. Pediat.*, 1945, clxv, 142.
7. AUSTIN, V. T., and QUASTLER, H.: Idiopathic (?) hypoprothrombinemia. Report of a case, *Am. Jr. Med. Sci.*, 1945, ccx, 491.
8. QUICK, A. J.: Effect of synthetic vitamin K and of quinine sulfate on prothrombin level, *Jr. Lab. and Clin. Med.*, 1946, xxxi, 79.
9. FASHENA, G. J., and WALKER, J. N.: Salicylate intoxication; studies on effects of sodium salicylate on prothrombin time and alkali reserve, *Am. Jr. Dis. Child.*, 1944, lxviii, 369.
10. AGGELER, P. M., LUCIA, S. P., and FISHBON, H. M.: Purpura due to vitamin K deficiency in anorexia nervosa, *Am. Jr. Digest. Dis.*, 1942, ix, 227.
11. AGGELER, P. M.: Personal communication.
12. LINK, K. P., OVERMAN, R. S., SULLIVAN, W. R., HEUBNER, C. F., and SCHEEL, L. D.: Studies on the hemorrhagic sweet clover diseases. Hypoprothrombinemia in the rat induced by salicylic acid, *Jr. Biol. Chem.*, 1943, cxlvi, 463.
13. COOMBS, F. S., JR., HIGLEY, C. S., and WARREN, H. A.: Magnitude of salicylate hypoprothrombinemia, *Proc. Central Soc. Clin. Res.*, 1945, xviii, 68.
14. BUTT, H. R., et al.: Studies in rheumatic fever; physiologic effect of sodium salicylate on human being, with particular reference to prothrombin level of blood and effect on hepatic parenchyma, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1195.
15. MEYER, O. O., and HOWARD, B.: Production of hypoprothrombinemia and hypocoagulability of the blood with salicylates, *Proc. Soc. Exper. Biol. and Med.*, 1943, liii, 234.
16. RAPOPORT, S., WING, M., and GUEST, G. M.: Hypoprothrombinemia after salicylate administration in man and rabbits, *Proc. Soc. Exper. Biol. and Med.*, 1943, liii, 40.
17. STEVENS, D. L., and KAPLAN, D. B.: Salicylate intoxication in children; report of 4 cases, *Am. Jr. Dis. Child.*, 1945, lxx, 331.
18. TROLL, M. M., and MENTEN, M. L.: Salicylate poisoning; 4 cases, *Am. Jr. Dis. Child.*, 1945, lxix, 37.
19. RAPOPORT, A. E., NIXON, C. E., and BARKER, W. A.: Fatal secondary toxic thrombocytopenic purpura due to sodium salicylate; report of a case, *Jr. Lab. and Clin. Med.*, 1945, xxx, 916.

20. ASHWORTH, C. T., and McKEMIE, J. F.: Hemorrhagic complications with death probably from salicylate therapy; 2 cases, Jr. Am. Med. Assoc., 1944, cxxvi, 806. Note by QUICK, A. J.: Jr. Am. Med. Assoc., 1944, cxxvi, 1167.
21. BRINKHOUS, K. M.: Plasma prothrombin; vitamin K, *Medicine*, 1940, xix, 329.
22. ESTREN, S., MEDAL, L. S., and DAMESHEK, W.: Pseudohemophilia, *Blood*, 1946, i, 504.
23. FARBER, J. E.: A familial hemorrhagic condition simulating hemophilia and purpura hemorrhagica, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 815.
24. DE GENNES, L., MAHODEAU, D., and LAUDAT, M.: Severe acidosis-ketosis with purpuric syndrome due to sodium salicylate; recovery following dextrose-insulin therapy, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1943, lviii, 375.
25. KARK, R., and SOUTER, A. W.: Hypoprothrombinemia and avitaminosis-K in man, *Brit. Med. Jr.*, 1941, ii, 190.
26. LUCIA, S. P., and AGGELER, P. M.: Treatment of dicoumarol-induced hypoprothrombinemic hemorrhage with vitamin K<sub>1</sub> oxide, *Proc. Soc. Exper. Biol. and Med.*, 1944, lvi, 36.
27. RHOADS, J. E., WARREN, R., and PANZER, L. M.: Experimental hypoprothrombinemia, *Am. Jr. Med. Sci.*, 1941, ccii, 847.
28. RICHARDS, R. K., and SHAPIRO, S.: Experimental and clinical studies on action of high doses of hykinone (menadione bisulfite) and other menadione derivatives (including use to counteract prothrombinemia caused by salicylates in rheumatic endocarditis), *Jr. Pharmacol. and Exper. Therap.*, 1945, lxxxiv, 93.
29. LUCIA, S. P.: Personal communication.

## POTASSIUM DEFICIENCY ASSOCIATED WITH DIABETIC ACIDOSIS \*

By PETER E. TUYNMAN, M.D.,† and SEYMOUR K. WILHELM, M.D.,‡  
*Detroit, Michigan*

THE clinical syndrome relative to an abnormally low concentration of serum potassium has been definitely associated with certain cases of diabetic acidosis.

Three cases of hypopotassiumemia following diabetic acidosis have been reported, one case by Holler<sup>1</sup> and two cases by Nicholson and Branning.<sup>2</sup> In these three cases there was good response to therapy of the acidosis, only to be followed shortly by generalized muscular weakness accompanied by progressive respiratory difficulty. In each case the potassium concentration of the serum was found to be decreased and in the two cases which received potassium the clinical response was striking. The third patient received no potassium and died in collapse 37 hours after admission, although the blood sugar and serum carbon dioxide combining power had been normal for 12 hours.

Nicholson and Branning suggest that five deaths in the Duke Hospital acidosis series were due to potassium deficiency although no laboratory determinations of potassium had been performed.

In presenting this case, we wish also to suggest that the syndrome of potassium deficiency following diabetic acidosis occurs more frequently than is sus-

\* Received for publication January 24, 1948.

From the Department of Internal Medicine, Mount Carmel Mercy Hospital.

† Assistant Resident in Medicine.

‡ Senior Resident in Medicine.

pected and that its recognition may bring about a notable decrease in the present mortality rate in diabetic acidosis.

It is not the purpose of this paper to present a review of potassium metabolism. However, it is necessary to describe a few of the concepts of potassium metabolism which are pertinent to the case presented.

Potassium is the major base of intra-cellular elements, and plays the rôle of counterpart to extra-cellular sodium. Potassium within the cells serves the same general functions relative to osmotic pressure regulation and acid-base balance as does sodium in extra-cellular fluids. The normal serum potassium level ranges between 16 and 22 milligrams per 100 c.c. of serum.

It is generally accepted that potassium ions play an important part in the transmission of nerve impulses and in synaptic transmission. Opinions upon the exact functions of potassium in these respects are still controversial. It is probable that the deficiency of potassium within and about motor nerves produced the picture of muscle fatigue encountered in the reported cases and in our study.

Allott and McArdle<sup>3</sup> in a study of three cases of periodic familial paralysis showed that attacks of paralysis, clinically identical with a natural attack, would be produced by the administration of glucose by mouth, by insulin, and more consistently by glucose and insulin together. Weakness developed when the potassium level of the serum reached 12 milligrams per cent and the complete picture of severe generalized muscle weakness appeared at a concentration of 10 milligrams per cent. All three cases of periodic familial paralysis responded to potassium chloride orally. Potassium balance experiments disclosed that potassium was not lost through diuresis but that probably it entered the tissues. Allott and McArdle believe that in this disease there exists a periodically increased demand for potassium by the muscles. The body attempts to gratify this demand by withdrawing potassium from the serum and by diminishing the excretion of potassium.

Fenn<sup>4</sup> showed that potassium is an especially mobile element within the body. Acid-base imbalances cause shift of potassium ions in or out of cells. Potassium migrates from cells to plasma in conditions involving an excessive excretion of sodium chloride and water. Thus, diabetic acidosis, as well as the parenteral administration of large quantities of glucose solution are two conditions causing this shift of potassium from intra-cellular spaces to plasma. Fenn also contends that the deposition of water and potassium within the liver cells is a prerequisite of glycogenesis, indicating that during the treatment of diabetic acidosis potassium would be withdrawn from the plasma and deposited in the liver.

Castleden<sup>5</sup> concluded that three methods of decreasing serum potassium concentration are administration of glucose, injection of insulin and injection of adrenalin. With the administration of glucose and insulin he associated the decrease of serum potassium concentration with the passage of sugar from blood into tissues.

Atchley, Loeb and associates,<sup>6</sup> in studies upon the withdrawal and reestablishment of insulin in diabetic patients, drew the following conclusions. During initial glycosuria, preceding development of acidosis, there occurs a loss of intra-cellular and extra-cellular body fluids accompanied by their constituent electrolytes. The excretion of water and electrolytes tended to seek a level during the pre-acidosis glycosuria stage. As ketogenic acidosis developed a secondary in-

crease in excretion of water and electrolytes occurred, which continued until the acidosis was terminated by treatment. In the recovery state, after reestablishment of insulin, there was retention of intra-cellular and extra-cellular water and electrolytes.

### CASE REPORT

H. C., 51 year old female, was admitted to Mount Carmel Mercy Hospital at 3:30 a.m., August 20, 1947, in coma. History obtained from relatives disclosed that five months prior to admission the patient first noticed weight loss, which progressed to a total loss of 45 pounds from an original weight of 155 pounds. The weight loss was accompanied by polydipsia, polyphagia and a mild degree of polyuria. Three weeks prior to admission she consulted her physician and the diagnosis of diabetes mellitus was made. Hospitalization was urged at this time but refused by the patient, who also made little effort to adhere to her diet. Ten days prior to hospital admission, dyspepsia was noted, accompanied by a foul taste in the mouth, anorexia, and more severe polydipsia. On the evening preceding admission, the patient became stuporous and lapsed into coma at 11:00 p.m. There was no history of the patient ever having received insulin.

Physical examination at the time of admission revealed the patient to be in coma, but responsive to painful stimuli. Kussmaul breathing was evident and a definite odor of acetone was on the breath. There was a slight decrease of the intra-ocular pressure. The pupils were equal, of normal size and reactive to light. Corneal reflexes were present but sluggish. The skin was dry, the extremities cool. Temperature taken rectally was 99° F. Pulse rate was 140, regular and rhythmic. The blood pressure was 115 systolic, 70 diastolic. The heart and lungs were normal to auscultation and percussion. The abdomen and extremities were negative. There was a generalized hyporeflexia with no pathologic reflexes present. A catheterized urine specimen was strongly positive for sugar and acetone. The diagnosis of diabetes mellitus with acidosis and coma was made. Treatment was begun immediately, and consisted of the following: (1) Regular insulin, 25 units intravenously, 50 units subcutaneously. (2) One-sixth molar racemic sodium lactate, 1000 c.c., intravenously. (3) Indwelling catheter, urinalysis for sugar and acetone performed at half-hour intervals. (4) Regular insulin, 25 units subcutaneously at half-hour intervals until urine became acetone free. (5) Glucose, 5 per cent in saline, intravenously, continuously, until the patient was able to take fluids by mouth. Five hundred cubic centimeters of 10 per cent glucose in saline was given when the glycosuria decreased in the presence of persistent severe acetonuria. (6) Nasal oxygen. (7) External heat. (8) Gastric lavage with 5 per cent sodium bicarbonate solution, 250 c.c. of which was left in the stomach.

The patient regained consciousness at 6:15 a.m., three hours after admission, after having received 175 units of regular insulin. At this time the respiratory rate was 34 per minute, pulse 140, blood pressure 120 mm. Hg systolic, 75 diastolic. Kussmaul type of respirations persisted. Nasal oxygen was discontinued and the patient was placed in an oxygen tent.

At 8:15 a.m., by which time 275 units of insulin had been administered, the blood sugar was 376 milligrams per cent, the serum carbon dioxide combining power 25 volumes per cent. By 11:00 a.m., seven and one-half hours after admission, the blood pressure had dropped to 90 systolic, 60 diastolic, pulse rate was 88 per minute. Kussmaul respiration had ceased, and, although there was no objective evidence of labored breathing, the patient complained of respiratory distress and generalized weakness and requested to remain in the oxygen tent. Physical examination revealed no evident cause of the respiratory difficulty or of the weakness. At this time the

blood sugar was 356 milligrams per cent and the serum carbon dioxide combining power 37 volumes per cent. During these seven and one-half hours the patient had received 400 units of insulin, three liters of fluids parenterally and approximately one liter orally (figure 1).

Impairment of respiration gradually increased despite the administration of eight liters of oxygen per minute. The blood pressure remained in the vicinity of 90 systolic, 60 diastolic. By 6:00 p.m., 14 hours after admission, the patient had received 635 units of insulin and approximately six liters of fluids. Acetone was no longer present in the urine. At this time the serum potassium, as determined by the method of Kolmer and Boerner, was reported as 10 milligrams per cent, which is well below the minimum normal level.

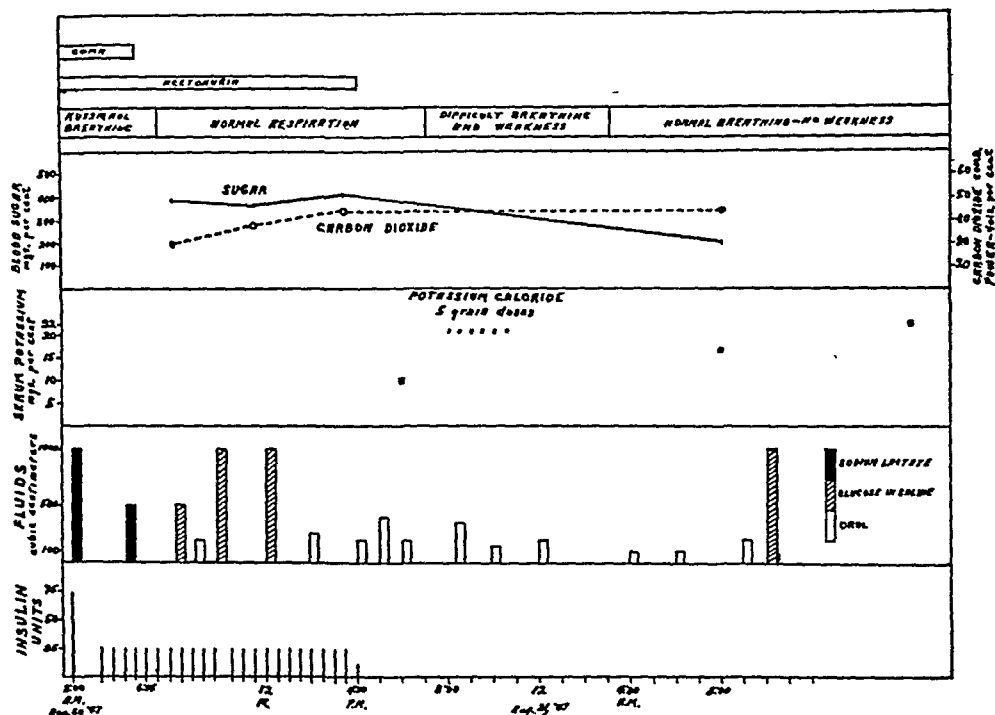


FIG. 1.

Potassium chloride was administered in five grain doses at half-hour intervals for six doses. Shortly after receiving the total dosage, the respiratory impairment was noticeably diminished and progressive improvement ensued. At 10:00 a.m., August 21, thirty-six hours after admission, the serum potassium level was 16 milligrams per cent, the lower limit of normal. The muscle weakness and respiratory distress had disappeared and the patient no longer needed oxygen.

Recovery thereafter was uneventful and the patient's diabetes was controlled. Later serum potassium levels were well within normal range.

Apparently several factors entered into the reduction of serum potassium in this previously untreated diabetic patient. These are: (1) Excretion of potassium accompanying extended glycosuria before the development of acidosis. (2) Increased potassium excretion during development of acidosis. (3) Loss of potassium by diuresis with copious amounts of fluid, five liters during 14 hours of treatment. (4) Withdrawal of potassium from serum and deposition

of the potassium in liver cells, caused by the administration of 635 units of insulin during treatment. (5) Relative decrease due to hemo-dilution with fluids.

In cases thus far reported, potassium deficiency associated with diabetic acidosis was recognized in the post-coma stage. It is not unreasonable that, in severe cases, it may develop and be the unsuspected cause of death during coma.

Case histories of diabetic deaths at Mount Carmel Mercy Hospital during the past eight years were reviewed. There were 25 cases in which acidosis of some degree was present although not the actual cause of death in the majority. In five cases there was suggestive evidence that the actual cause of death may have been potassium deficiency. Three of these cases exhibited favorable response to treatment of the acidosis, but collapse and death nevertheless ensued. Although no laboratory determinations of serum potassium had been performed, the clinical picture in these cases was strongly suggestive of potassium deficiency.

We believe that the recognition and treatment of potassium deficiency will play an integral part in decreasing the mortality rate in diabetic acidosis.

Potassium inhibition of the heart is known to occur when the heart is perfused with a solution containing potassium in excess, or potassium unaccompanied by calcium. The effect consists of a gradual increase of the duration of diastole until the heart comes to rest in a completely relaxed state.<sup>7</sup> Death from cardiac failure results when the serum potassium reaches a concentration four times its normal. Potassium ions are toxic when administered intravenously in high concentration. But there is no danger in the injection of potassium in concentrations normally characteristic of extra-cellular fluid. The potassium ions, if in excess, are rapidly excreted. However, where renal function is severely impaired, caution must attend the administration of potassium by any route. Large amounts of potassium have been administered orally without resulting in untoward reactions.<sup>8</sup> Potassium chloride may be given orally in doses of 5 to 10 grams in tablet form or in water. It may be injected intravenously in doses of 50 c.c. of a 2 per cent solution, taking at least ten minutes for the injection.<sup>9</sup> It is felt that in those cases of diabetic acidosis in which there occurs a low serum concentration of potassium the administration of the latter according to the recommended methods will not result in any degree of toxicity.

### SUMMARY

1. The syndrome of potassium deficiency has been discussed.
2. The relation of diabetic acidosis and its treatment to the production of potassium deficiency has been described.
3. A case of potassium deficiency associated with diabetic acidosis has been presented and its treatment and results described.
4. The recognition of this syndrome may be of definite aid in the reduction of mortality from diabetic acidosis.
5. Potassium toxicity is mentioned, with recommendations upon dosage and precautions to attend the administration of potassium.

### BIBLIOGRAPHY

1. HOLLER, J. W.: Potassium deficiency during the treatment of diabetic acidosis, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 1186.

2. NICHOLSON, W. M., and BRANNING, W. S.: Potassium deficiency in diabetic acidosis, Jr. *Am. Med. Assoc.*, 1947, cxxxiv, 1292.
3. ALLOTT, E. N., and MCARDLE, B.: Further observations on familial periodic paralysis, *Clin. Sci.*, 1937, iii, 229.
4. FENN, W. O.: Role of potassium in physiological processes, *Physiol. Rev.*, 1940, xx, 377.
5. CASTLEDEN, L. I. M.: The effect of adrenalin on the serum potassium level in man, *Clin. Sci.*, 1937, iii, 241.
6. ATCHLEY, D. W., LOEB, R. F., DICKINSON, W. R., JR., BENEDICT, E. M., and DRISCOLL, M. E.: On diabetic acidosis: detailed study of electrolyte balances following withdrawal and reestablishment of insulin therapy, Jr. *Clin. Invest.*, 1933, xii, 297.
7. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practice, 1945, Williams and Wilkins Co., Baltimore, 4th ed., p. 158.
8. GOODMAN, L., and GILMAN, A.: The pharmacological basis of therapeutics, 1941, Macmillan Co., New York, p. 597.
9. DUNCAN, G. G.: Diseases of metabolism, 1942, W. B. Saunders Co., Philadelphia, p. 267.

## PITUITARY IMPLICATIONS IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY \*

By WILLIAM BLOOM, M.D., *New York, N. Y.*

THE pathogenesis of chronic hypertrophic osteoarthropathy remains unsolved. The clinical entity is obscured rather than clarified by a multiplicity of unsatisfactory hypotheses.<sup>1</sup>

Within the last five or six years evidence has appeared in the literature that would seem to point to a more logical understanding of this uncommon disease. That the proper approach to this subject is an endocrine one may be suspected by emphasizing the common characteristics of three syndromes which may be confused clinically, viz.—acromegaly, pachydermiosis of Touraine and Gallé<sup>2</sup> and hypertrophic pulmonary osteoarthropathy. The first condition is of definite endocrine origin. The second is very often considered of endocrine origin. The last, though frequently confused with the former, is rarely so considered. It may be conceded that anoxia<sup>3</sup> and toxicity are important factors, if not the only factors, in the pathogenesis of clubbed fingers, since this condition is found in the presence of advanced pulmonary disease or chronic anoxia of cardiovascular origin. On the other hand, severe hypertrophic pulmonary osteoarthropathy frequently occurs in early pulmonary disease and often even before the pulmonary pathologic process can be clinically detected. It would appear, therefore, that these two conditions represent separate entities and that a common etiology and pathogenesis is very unlikely.

Because of inadequate knowledge regarding the origin and development of chronic hypertrophic pulmonary osteoarthropathy many synonyms have arisen which presumably represent stages of one clinical entity but which in all likelihood represent several different syndromes. It is to be hoped that further knowledge will separate these entities and regroup them in proper pathologic or etiologic relationships. Thus, E. A. Locke and A. Grollman<sup>4</sup> list a few of the

\* Received for publication February 5, 1946.



synonyms in vogue: (1) clubbed fingers, (2) hippocratic fingers, (3) essential dactylomegaly, (4) hypertrophic pulmonary osteoarthropathy, (5) Marie Bamberger's disease, (6) hyperplastic osteosis, (7) pachydermiosis, etc., etc. They define the condition as being characterized by painless, general, symmetrical clubbing of the fingers and toes, often associated with hypertrophy of the long bones of the forearms and legs. Often it is secondary to some chronic disease, particularly of the lungs. Mendelowitz<sup>5</sup> classifies the disease from the etiological standpoint into (1) The hereditary form (a rare, primary disease passed on as a

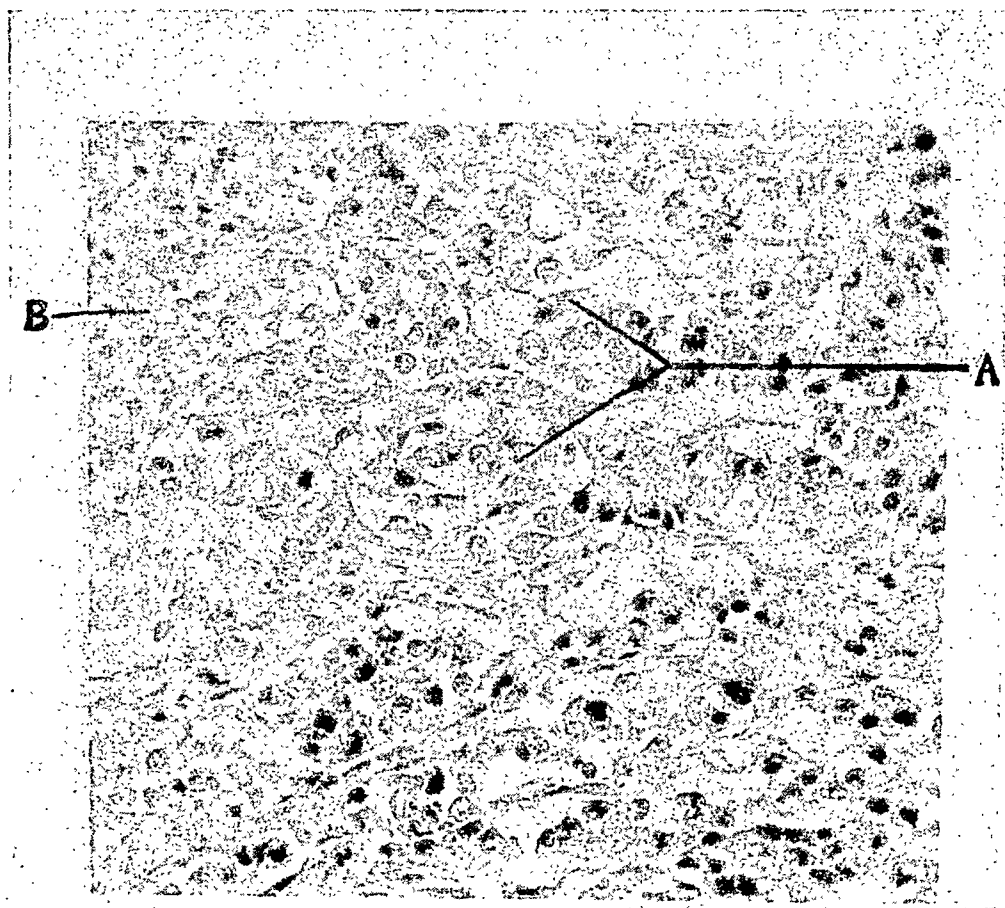


FIG. 1. Pituitary gland ( $\times 250$ ). Metastatic cancer at A is infiltrating the characteristic anterior lobe parenchyma (B).

Mendelian dominant type), (2) The idiopathic form in which there is no evidence of primary disease and no hereditary factor (this may be the same as that described by Touraine and Gallé), (3) The acquired form—(a) associated with pulmonary conditions such as tuberculosis, empyema, bronchiectasis, abscess, etc., (b) secondary to cardiac conditions such as congenital heart disease with cyanosis and subacute bacterial endocarditis, (c) following hypertrophic biliary cirrhosis, (d) following such gastrointestinal conditions as ulcerative colitis, dysentery, etc., (e) in association with miscellaneous diseases such as Raynaud's disease, cystopyelitis, purpura and polycythemia. Pathologically there is enlarge-

ment of the fingers and toes due to proliferation of the soft tissues and increase in thickness of the periosteum. Cyanosis of the fingers is very common. The hands may be enlarged to give the appearance of gigantism. Continuing with



FIG. 2. Appearance of patient on second admission showing fusiform enlargement of the long bones, hypertrophy of the right breast and large, spade-like hands, not unlike acromegaly.

the description of the disease, most authors include in the same category those cases which present (in addition to the above) severe subperiosteal bony proliferation associated with ossifying periostosis of the long bones. However, as indicated, it is likely that the more severe disease bears an entirely different

etiologic relationship. From the symptomatic standpoint, Sternberg<sup>6</sup> classifies the disease into three types: (a) clubbing of the fingers and toes without changes in the long bones (this is the most common type, symptoms are absent), (b) Von Bamberger's type—clubbing of the fingers and toes associated with painful thickening of the long bones especially the forearms and lower legs, (c) Marie's

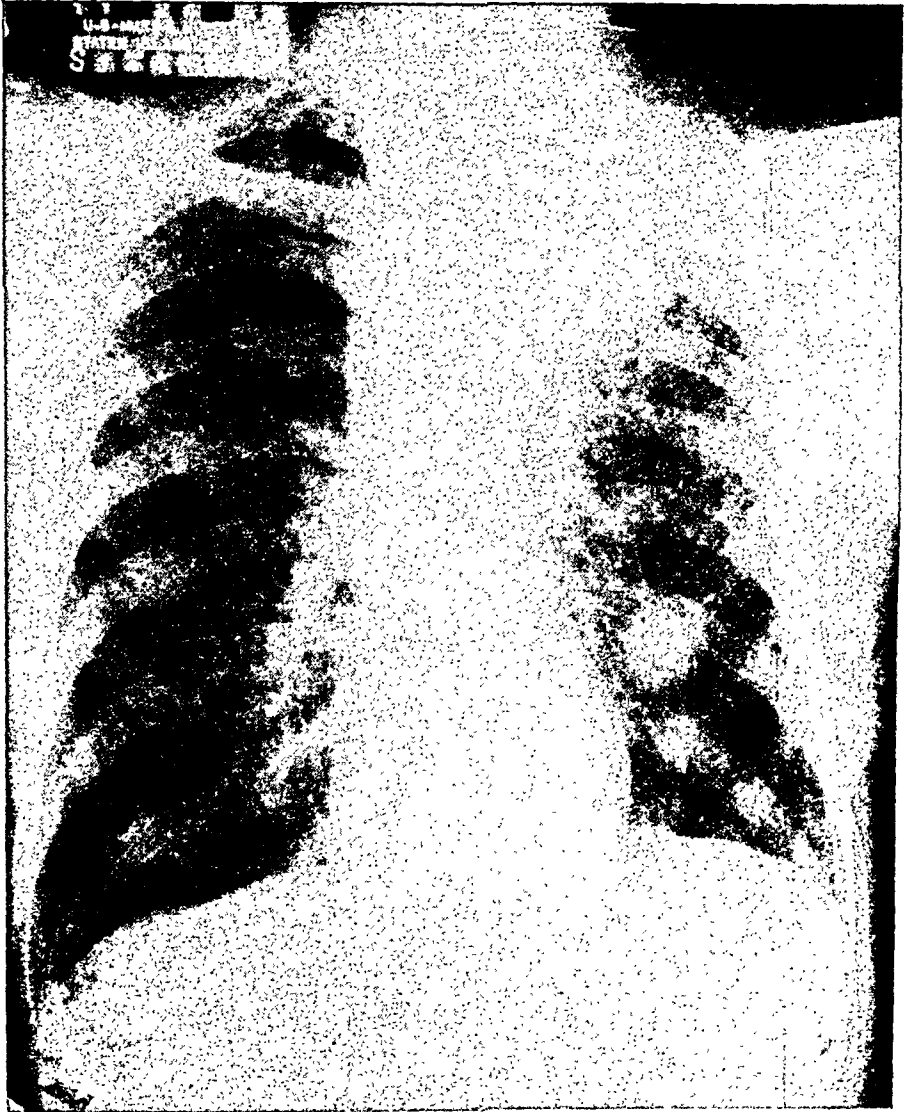


FIG. 3. Roentgenogram of the lungs showing bronchiogenic neoplasm in the apical and subapical portion of the left upper lobe with metastatic involvement of the lower lobe.

type—deformities are markedly conspicuous, severe and painful, and overshadow the primary disease found.

The trend of thought regarding the etiology and pathogenesis of this interesting syndrome has been away from existing concepts and in the direction of chemical or hormonal stimulation. In 1929 Crump<sup>7</sup> hypothesized "abnormal substance circulating in the blood which affects the periosteum of the bones, the joints and terminal phalanges as evidenced by clubbing of the fingers" (this could

conceivably be of hormonal origin). Tufting of the terminal phalanges of the fingers was regarded by Cushing<sup>8</sup> as pathognomonic of acromegaly. It is interesting to note that this finding is likewise present in hypertrophic osteoarthropathy. Forte,<sup>9</sup> Rogers,<sup>10</sup> Aschoff,<sup>11</sup> Fried<sup>12</sup> have at various times offered evidence in favor of the concept that the lungs are endowed with functions in addition to respiration suggesting a secretory action. Fried,<sup>13</sup> in an excellent article

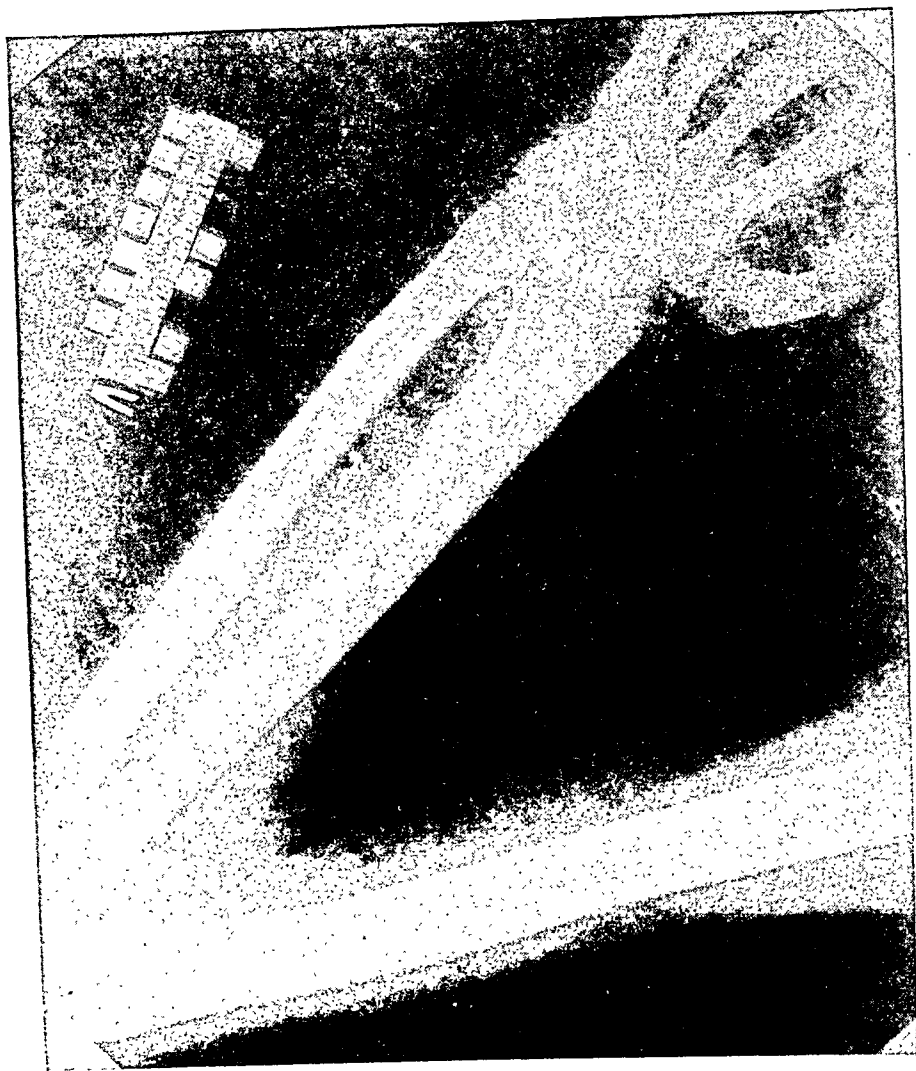


FIG. 4. Roentgenograms of the upper extremity showing ossifying periostitis with subperiosteal bone proliferation.

published in 1943, promulgates the concept that diffuse osteoarthropathy found in neoplastic disease of the lungs is in all probability caused not by toxins or circulatory disturbances but by endocrine imbalance akin to acromegaly and pachyderma with pachyperiostosis. To substantiate this hypothesis he presents three cases of chronic hypertrophic osteoarthropathy on whom autopsy revealed hyperplasia of the eosinophilic cells of the pituitary gland. He suggests the possibility that the stimulus to overdevelopment of the eosinophilic cells arose



FIG. 5. Spade-like enlargement of the hands with widening of the wrists and cylindrical deformity of the forearms.

FIG. 6. Marked cylindrical deformity of the ankles and legs.

from some endocrine factor inherent in the lungs. In the case to be presented metastasis to the pituitary gland was found. It is suggested that the metastatic lesions acted as a stimulant to excessive secretion of pituitary hormone, giving rise to the osseous syndrome in much the same manner as acromegaly. In support of this concept, attention may be called to hypertrophy of the breasts asso-

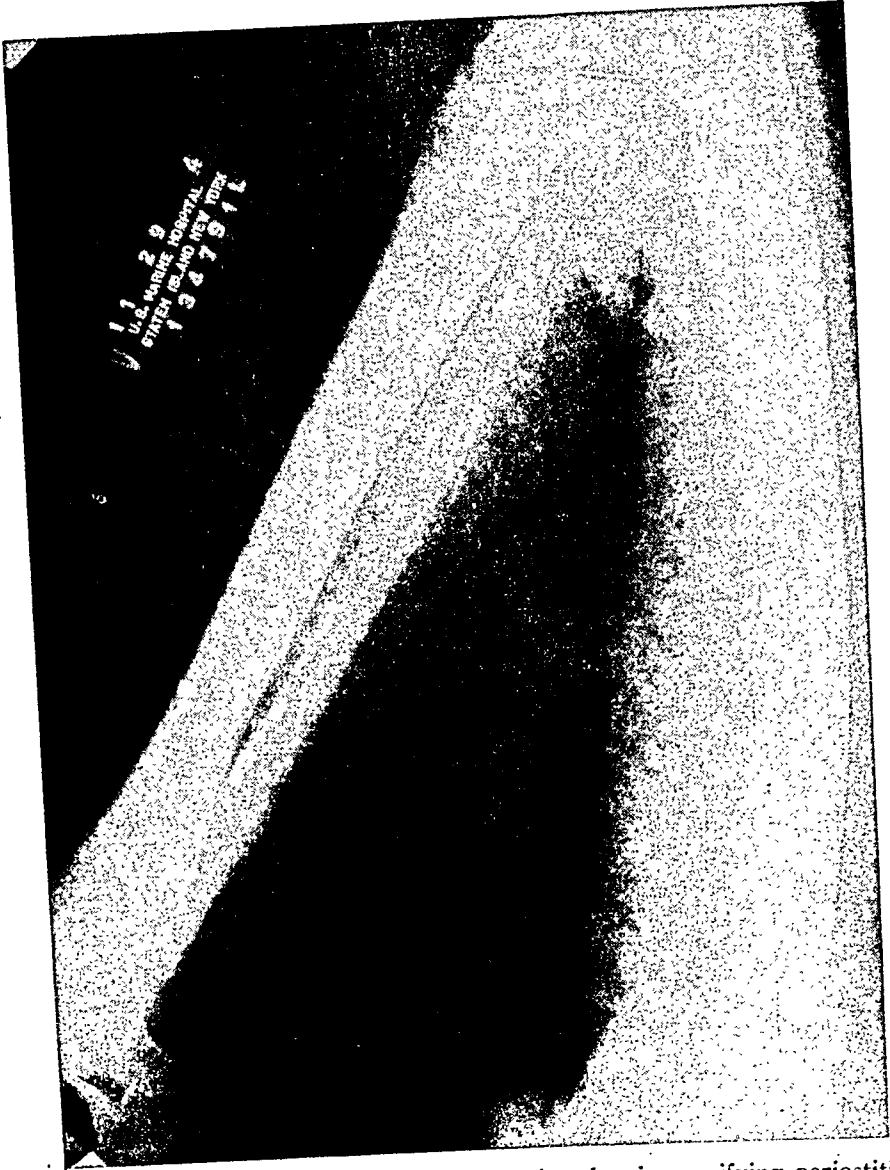


FIG. 7. Roentgenograms of the lower extremity showing ossifying periostitis with subperiosteal bone proliferation.

ciated with this disease as reported by Bamberger, Fried and present in the case to be described. In addition, Fried's case also presented multiple cysts of the adrenal cortex. Ryneerson and Sacasa<sup>14</sup> report the condition developing in a patient operated on for hyperthyroidism. This patient developed postoperative hypothyroidism with progressive exophthalmus. There were no lung lesions. Thomas<sup>15</sup> described a similar case without lung lesions. Both of these cases are

in many ways similar to the syndrome described by Touraine and Gallé<sup>2</sup> and implicate the pituitary gland.

### CASE REPORT

The patient, a 51 year old white male merchant seaman (cook), was admitted to the Medical Service for the first time on November 5, 1943 complaining of severe pain in both hands and feet and in the left shoulder. The pain in the left shoulder radiated down the left arm. There was increasing pain and limitation of motion in the joints of both extremities. These symptoms had been present and progressive for three months and were aggravated by cold weather. There was no cough or expectoration and no marked weight loss. He stated that his fingers were large since childhood but that the joint involvement was of recent onset. One month prior to admission he became aware of painful enlargement of both breasts.

Physical examination revealed a rather well-developed and nourished white male presenting marked enlargement of all the joints with cylindrical deformity of the long bones of the forearms and legs. There was extensive clubbing of the fingers. The breasts were enlarged and tender. His general appearance was not unlike that of an acromegalic. There was profuse sweating of the hands and feet, more marked on the left side. The remainder of the physical examination was not remarkable. The lungs were negative to percussion and auscultation; no râles were heard. Urinalysis, blood count and Wassermann test were negative. Roentgenogram of the lungs revealed an homogeneous density in the left upper lobe to the left of the trachea, with some linear strands of increased density to the apex. This was interpreted as an old acid fast lesion, probably inactive. Repeated sputa examinations were negative for acid fast bacilli except on one occasion when rare acid fast bacilli were thought to be present. Following this report, however, concentrated sputa, gastric specimens and guinea pig inoculations were negative for tuberculosis. Roentgen studies of the long bones and of the hands and feet revealed evidence of far advanced hypertrophic pulmonary osteoarthropathy with periosteal thickening and beginning flexion deformities of the joints of the fingers. Roentgenograms of the skull showed no abnormality of the sella turcica. Sedimentation rates were persistently elevated. Blood uric acid was 3.8 mg. per cent; serum calcium 11 mg. per cent; phosphorus 3.8 per cent; alkaline phosphatase 3.4 Bodansky units and acid phosphatase was 1.2 Bodansky units.

His course in the hospital was slowly progressive, with weight loss and persistent, severe joint pains which were unrelieved by symptomatic therapy. He remained in the hospital for eight months during which time serial roentgenograms revealed no progression of the pulmonary lesion. He was discharged, unimproved, on August 28, 1944 but was re-admitted on October 30, 1944 in a markedly emaciated state with evidence of an early Horner's syndrome on the left side. In the interim following discharge he had developed a productive cough, increasing in intensity. He complained bitterly of joint and bone pains. A roentgenogram of the lungs on this occasion revealed marked extension of the lesion previously reported, obviously malignant. There was a chain of firm, non-movable lymph nodes in the anterior triangle of the neck. Roentgenographic studies of the long bones indicated increased periosteal thickening and subperiosteal new bone formation, greater in extent than previously reported. His course was progressively downward and he died on May 31, 1945, seven months after the second admission.

### *Autopsy Findings*

Significant findings on postmortem examination, in addition to the pathological changes of the osseous system, were limited to the lungs and pituitary gland. The

left lung weighed 810 grams, the upper lobe was stony hard in consistency and the overlying pleura was thickened with gray fibrous tissue. The lower lobe was crepitant and revealed two small nodules, palpable deep within its substance. The cut section of the left upper lobe revealed almost complete infiltration with confluent masses of gray-black or yellow-gray tumor, irregular fibrous strands interlaced throughout. No normal parenchyma was present in this lobe. On microscopic examination several large zones of neoplastic infiltration were observed with definite acinar grouping. The cells showed a columnar pattern with clear or acidophilic cytoplasm. Nuclei were frequently of large and irregular form and pattern. The bronchial walls were invaded. There were many foci of neutrophils in areas of necrosis and abscess formation. The peribronchial lymph nodes were heavily infiltrated by masses of tumor cells.

The brain weighed 1380 grams, its surface was smooth, its convolutions normal. The ventricular systems appeared normal and the sella turcica was of the usual size. The pituitary gland revealed no gross abnormalities but on section a large metastatic focus of neoplasm was found in the anterior lobe. The cells were irregular in solid cords and clusters and vaguely columnar.

#### SUMMARY

1. The subject of hypertrophic pulmonary osteoarthropathy is discussed from the standpoint of etiology and pathogenesis. The need for a logical classification is suggested. Several separate entities are implied which heretofore have been grouped as one disease.

2. Reference is made to the literature, particularly to the work of Fried, pointing to an endocrine basis for this osseous syndrome.

3. Fried's views implicate the pituitary gland as the source of the deranged osseous picture. He suggested a hormonal relationship between the lungs and the pituitary gland.

4. A case is presented which revealed metastasis to the pituitary glands, secondary to lung carcinoma.

#### CONCLUSIONS

1. A case of carcinoma of the lung with chronic hypertrophic pulmonary osteoarthropathy is presented in which metastasis to the anterior lobe of the pituitary gland was found.

2. This case suggests that the overstimulation of the anterior lobe of the pituitary gland by the metastatic lesions was responsible for the picture of hypertrophic osteoarthropathy, thus further enhancing the view that the pituitary gland is responsible for the osseous lesions.

3. Further studies are indicated to establish the etiology of this condition and to separate it from apparently non-related conditions such as clubbed fingers, etc.

#### BIBLIOGRAPHY

1. Prognostic No. 17, Loeb's Classical Library, 1923, ii, 25.
2. TOURAINE, A., SOLENTE, G., and GALLÉ, L.: Une syndrome osteodermopathique: la pachydermi plicaturée avec pachyperostose des extrémités, *Presse méd.*, 1935, xcii, 1820-1824.
3. PIGEAX, D. M.: Recherches nouvelles sur l'étiologie, le symptomatologie et le mécanisme du développement fusiforme de l'extrémité des doigts, *Arch. gén. de méd.*, 1932, xxix, 174.



4. LOCKE, A. E.: Secondary hypertrophic pulmonary osteoarthropathy, *Oxford System of Medicine*, Vol. iv, part 3, p. 453.
5. MENDELOWITZ, M., and LESLIE, A.: Clubbing and hypertrophic osteoarthropathy, *Medicine*, 1942, xxi, 269.
6. STERNBERG, M.: Die Akromegalie, *Nothnagel's Handb. spez. Path. u. Therap.*, 1933, vii, Pare II, 72, li, 573.
7. CRUMP, C.: Histologie der allgemeinen Osteophytose, *Virchow's Arch. f. path. Anat.*, 1929, cclxxi, 467-511.
8. CUSHING, F. H.: "Club fingers" and hypertrophic pulmonary osteoarthropathy, *Internat. Clin.*, 1937, ii, 200-205.
9. FORTE, A. J. A.: Anatomie et physiologie, du poumon considéré comme organe de sécrétion, 1867, A. Delahaze, Paris.
10. ROGERS, G. H., and BENET, L.: Recherches sur la physiologie du poumon, *Rev. de méd.*, 1925, xlii, 1-20.
11. ASCHOFF, L.: Bemerkungen zur Physiologie des Lungengewebes, *Ztschr. f. d. ges. exper. Med.*, 1926, 1, 52-63.
12. FRIED, B. M.: Defensive and metabolic apparatus of lungs, *Arch. Path.*, 1928, vi, 1008.
13. FRIED, B. M.: Chronic pulmonary osteoarthropathy, dyspituitarism as a probable cause, *Arch. Int. Med.*, 1943, lxxii, 565-580.
14. RYNEARSON and SACASA: *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 353.
15. THOMAS, H. M., JR.: Acropachy; secondary subperiosteal new bone formation, *Arch. Int. Med.*, 1933, li, 571-588.

---

## HYPERTENSION CAUSED BY UNILATERAL KIDNEY DISEASE (A FOLLOW-UP REPORT) \*

By J. SHIRLEY SWEENEY,† M.D., Sc.D., F.A.C.P., and JOHN M. PACE,  
M.D., F.A.C.S., *Dallas, Texas*

IN the December 1943 edition of this Journal, we reported a case of hypertension caused by unilateral kidney disease.<sup>1</sup>

The patient (M. J. M.) was at that time unmarried, aged 21, and consulted one of us (J. S. S.) on May 3, 1941. She was referred by her family physician because of high blood pressure. Her family history was entirely negative. Her menstrual history, likewise, was perfectly normal. The only illness that she had had during childhood was measles. She stated that she had had some sort of kidney trouble, the nature of which was not clear; however, she remembered having been in bed for several days, but denied that there was any edema or blood in the urine. She had had an occasional attack of tonsillitis. Her tonsils and adenoids had been removed in 1940. She had had an appendectomy for acute appendix at the age of 13.

Her complaint, when she was first seen, was that of headache. She further stated that she had not felt well for the preceding six or seven months, having noticed fatigue and general malaise especially. Her headaches were basal in location, and were present each morning on awakening. In the latter part of 1940, she developed an upper respiratory infection. The physician who attended her took her blood pressure and found it to be 230 mm. Hg systolic and 120 mm. diastolic. From this time until she was first seen by one of us (J. S. S.), she had lost 12 pounds, was quite nervous, and complained of considerable fatigue in addition to her headaches.

\* Received for publication April 18, 1947.

† Medical Director, The Sweeney Diabetic Foundation, For the Study and Treatment of Diabetes and Allied Metabolic Disorders, Gainesville, Texas.

Her physical examination was essentially negative, except for some slight brownish pigmentation about her face, neck and forearms. There was some tortuosity of the retinal vessels and there were a few angiospastic areas noted on ophthalmoscopic examination. The arteries were moderately narrowed and there was some loss of light reflexes. Heart sounds were good, but forceful, with accentuation of the aortic second sound. The pulse rate was 100. Her pelvis was entirely negative, as was the rectal examination. Her extremities were cool, discolored and moist. Her blood pressure at the time of this examination was 224 mm. Hg systolic and 154 mm. diastolic. Laboratory studies included lateral stereoroentgenogram of the skull, blood chemistry, urea clearance, phenolsulfonphthalein kidney function, perirenal air studies, and a scout film of her abdomen. All of these studies were negative except that in the latter film there was noted a rather small kidney on the right side. She was then seen by one of us (J. M. P.) to be studied urologically. A catheterized



FIG. 1. Preoperative films May 1941.

(a) Right retrograde pyelogram: Small kidney outline with normally appearing pelvis and calices.

(b) Excretory urograms: Left—Slight hypertrophy of kidney with normal architecture of the pelvis and calices. Right—Good visualization in a small kidney.

urine was found to contain a small amount of albumin and granular casts. Cystoscopic examination was performed and indigo carmine was returned from the left ureteral orifice in a grade three concentration in 10 minutes, whereas only a faint trace of blue was noted from the right ureteral orifice. A retrograde pyelogram of the right side revealed a small kidney outline approximately one-half the size of the opposite kidney with a normal pelvis and calices. The left retrograde pyelogram was considered quite normal (figure 1a). Cystoscopy was repeated on the following day with the same findings as to the return of the indigo carmine. About 10 days later excretory urograms were made and good visualization was obtained of each kidney in 5, 15, and 25 minute films (figure 1b). About two weeks later the patient was subjected to another cystoscopy. Phenolsulfonphthalein was used intravenously and at the end of 45 minutes' time 22 per cent of the dye was returned from the left kidney and none from the right. This patient was observed for approximately two months,

particular attention being paid to eye grounds and blood pressure. Her systolic pressure ranged from 210 to 240 mm. Hg and the diastolic level varied from 120 to 140 mm. Hg.

About the middle of June 1941, there was noted a bit of fuzziness about the discs. At this time the patient complained also of mild visual disturbance. She was told that the right kidney was functionless and that she had possibly something to gain and nothing to lose by having it removed. She elected to have the operation, and on July 8 a nephrectomy was done on the right side.

The kidney removed was approximately one-third its normal size. When the patient was returned to her room following the operation, her blood pressure was 145 mm. Hg systolic and 85 mm. diastolic. Four hours later it was found to be 132 mm. Hg systolic and 100 mm. diastolic. The following morning her tension was 130 mm. systolic and 78 mm. diastolic. Twelve days later when she was discharged, the reading was 126 mm. systolic and 78 mm. diastolic.

The kidney grossly was considerably smaller than normal. It measured 10 by 4 by 3 cm. and weighed 60.6 grams. The capsule was thickened but stripped readily and underneath there was a smooth shiny surface. On section the cortex and medulla were very well defined. The cortex averaged 4 mm. in thickness. There was no gross scarring in the parenchyma. The kidney pelvis was not enlarged. There were no stones.

Microscopically, sections through different portions of the kidney revealed very extensive focal chronic inflammatory changes immediately beneath the capsule. In these areas was seen marked condensation of renal tissue with patchy scarring and with loss of tubules and glomeruli. A heavy small mononuclear cell infiltration occurred in these areas. Glomeruli in different states of degeneration were noted, whereas in striking contrast in the remainder of the renal parenchyma the glomeruli were essentially normal. The sectioned blood vessels were noticeably thickened, their lumina being reduced as much as one-third in diameter in numerous areas (see photomicrographs in original article). A section through the pelvis of the kidney revealed slight overgrowth of the pelvic mucosa. A few scattered chronic inflammatory cells were noted beneath. The pathologist, Dr. John L. Goforth, rendered the opinion that there was a chronic active progressive subcapsular pyelonephritis of marked degree.

The patient was seen on numerous occasions following her operation. Approximately two months following operation her eye grounds were strikingly different from the preoperative condition. The fuzziness had entirely disappeared about her discs; there was definite return of some light reflex; and the spasm previously noted was absent.

Her blood pressure varied from 110 to 116 mm. Hg systolic with a diastolic of 72 to 78 mm. The patient gained 15 pounds and went back to her work. She was carefully checked in February 1942, at which time her blood urea nitrogen was 10 mg. per 100 c.c. and her urea clearance was 124 per cent of normal. Repeated urine examinations revealed nothing of consequence. Phenolsulfonphthalein excretion was 50 per cent in the first hour and 9 per cent in the second.

This patient presented only one interesting symptom following her operation, which was that of a momentary dizziness on arising from a recumbent position. This dizziness was rather marked a few months following operation but gradually became less severe, and when last seen the patient was entirely free of this annoyance. The explanation we suggest for this interesting symptom is the obvious lack of cardiac and vascular adaptation to the changed levels of blood pressure. She has subsequently been observed for any possible disease in the remaining kidney.

July 8, 1947, will complete six years postoperative observation. During the six years, the patient has married and now has a child three years of age. She went through her pregnancy with no difficulty, giving birth to a 7½ pound baby. Her

maximum blood pressure reading during her gestation and delivery was 122 mm. over 82 mm. Most of the readings varied from 106 to 110 mm. systolic. Her kidney function remained quite normal throughout the period of her pregnancy.

She was seen on January 25, 1947, by one of us (J. M. P.), complaining of some frequency and dysuria of five days' duration. She also stated that three years previously she developed some slight tenderness in the region of the left kidney, which usually manifested itself a few days before each menstrual cycle, only to disappear after the onset of menstruation. She stated that she never noticed it between her menstrual cycles.

Examination on January 25, 1947, revealed that her blood pressure was 120 mm. systolic and 82 mm diastolic. A catheterized urine was negative except for 1 plus

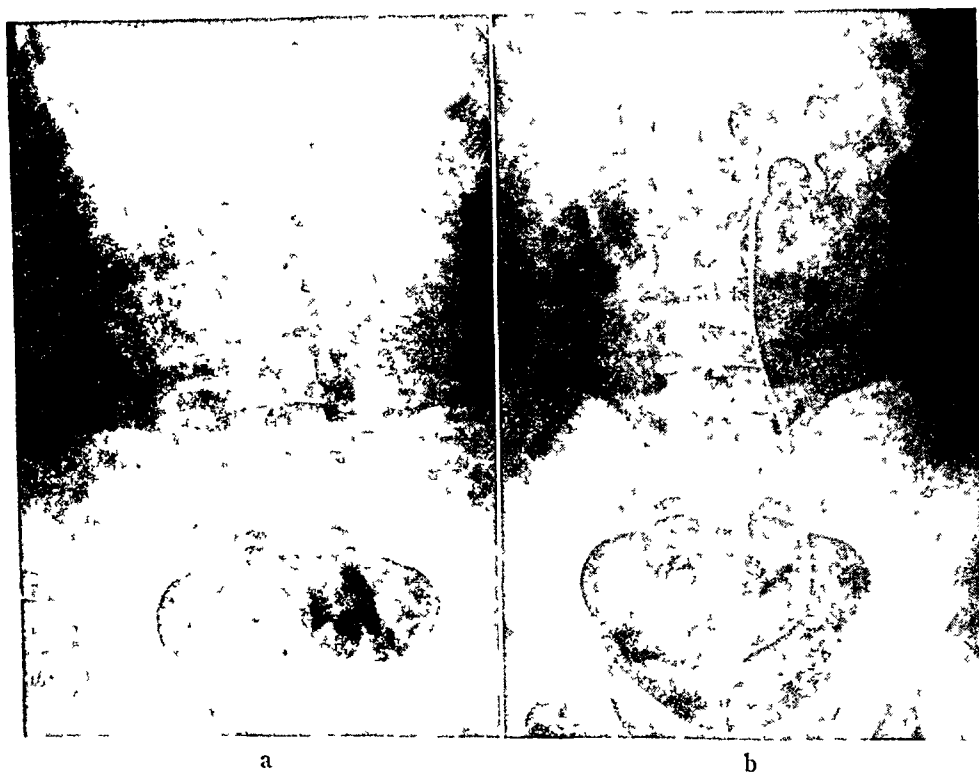


FIG. 2. February 1947.

- (a) Excretory urograms. Good function in remaining left kidney.
- (b) Left retrograde pyelogram. Pelvis and calices presented no abnormalities.

pus with gram negative bacilli. A cystoscopic examination revealed some diminution in the expulsive force of the bladder. A few fine trabeculations were noted on the posterior wall of the bladder. A catheter was passed into the left ureter with no obstruction and a pyelogram was made. There was some slight granulation tissue in the neck of the bladder. The retrograde pyelogram was interpreted as being within normal limits (figure 2b). At this time the patient was placed on ammonium chloride and mandelic acid by mouth. She returned for observation on February 14. On this date she had no bladder symptoms whatsoever, a catheterized urine stain was entirely negative, and a gram stain likewise was negative. Indigo carmine was returned in grade 4 concentration from the left kidney in six minutes. Excretory urograms were made at this time, and a normal function was found in the left kidney,

with some slight dilatation and tortuosity of the upper left ureter (figure 2a). Her blood pressure on February 14, 1947, was 118 mm. Hg systolic and 82 mm. diastolic. She stated that she was feeling exceedingly well and asked whether or not she might become pregnant again. She was advised that, whereas she had come through one pregnancy with no difficulty and has a child of three years, it would be, in our opinion, taking a little bit of risk to add another pregnancy.

### SUMMARY

This case has now been followed for seven years. She has had one pregnancy and has a perfectly normal child three years of age, and is maintaining a very normal blood pressure. It was thought of interest to review the findings on this patient, insofar as she had been followed closely and it would seem has been completely cured of her hypertension by removal of a small diseased right kidney.

We are cognizant of the danger inherent in reporting such a case as this, insofar as nephrectomy in hypertension might be too easily assumed to be a cure for hypertension. We feel that all younger individuals, that is, those individuals under the age of 40, who present themselves with a marked elevation of blood pressure, should be thoroughly investigated as to possible kidney disease, especially unilateral. Even when this is found, we further feel that the patient should be most carefully observed for a reasonable period of time before resorting to surgery. This period of observation should convince the clinician that there is no residuum of nor present pathology in the opposite kidney. Finally, it is our conviction that the operation should be placed on more or less of an elective basis, explaining to the patient that surgery might bring about a cure, but, insofar as some of the cases that have been operated upon in the past have not done too well, it is only fair that the patient should be so informed. We are, because of the case presented in this article, convinced that there does exist an occasional individual with marked hypertension which is attributable to unilateral kidney disease.

### BIBLIOGRAPHY

1. SWEENEY, J. SHIRLEY, and PACE, JOHN M.: Hypertension caused by unilateral kidney disease, *Ann. Int. Med.*, 1943, xix, 1013-1017.

---

### RUPTURE OF AMYLOID SPLEEN \*

By FREDERICK H. KING, M.D., F.A.C.P., and GORDON D. OPPENHEIMER, M.D.,  
*New York, N. Y.*

PRIMARY amyloidosis is an infrequent clinical entity and the search for possible etiological factors presents an interesting theoretical problem. Because of these considerations, as well as the fact that this case presents a unique series of events, an instance of this type of amyloidosis is detailed.

\* Received for publication March 14, 1946.

From the Medical Service of Dr. George Baehr and the Surgical Service of Dr. John H. Garlock, The Mount Sinai Hospital, New York City.

## CASE REPORT

The patient, a 36 year old married white woman, was first seen by one of us (F.K.) because of a mild sore throat and upper respiratory infection. She was obsessed with the possibility of a "streptococcus sore throat" and called a physician for reassurance. Her rectal temperature was found to be 99.2° F. and examination of the throat disclosed only slight redness of the anterior faucial pillar on one side. Moreover, it seemed that most of this inflammation could have been caused by the application of argyrol which the patient had adopted as a therapeutic measure. In the course of further physical examination it was noted that her complexion was sallow. The heart and lungs were found to be relatively normal. The blood pressure was 140 mm. Hg systolic and 90 diastolic. The pulse rate was slightly accelerated. Examination of the abdomen to which, incidentally, the patient objected on the grounds of irrelevance, disclosed the presence of a markedly enlarged liver reaching down to the iliac crest, The liver edge extended from the right iliac crest across the epigastrium at a level of about four or five fingers below the xiphoid and into the left upper quadrant. In the latter area a firm smooth spleen was felt which extended to about four fingers below the left costal margin. There was no lymphadenopathy.

By the disclosure of a hepato-splenomegaly the aspect of the case was entirely altered. Interrogation failed to elicit any relevant complaints. She had not lost weight. There were no gastrointestinal symptoms. There was no history of jaundice or of purpuric manifestations.

The patient's family was informed that it would be advisable to have a hematologic study. Without any prejudgment of the etiology of the hepato-splenomegaly it was felt that this study constituted the first diagnostic approach. It was emphasized that the mild sore throat, in all probability, had no relation to the finding of a hepato-splenomegaly and that all methods of investigation should be exhausted in an attempt to discover the cause. On the following day the patient sought other advice and was told that she had infectious mononucleosis but that leukemia had been excluded. It seemed difficult to accept the diagnosis of mononucleosis as the cause of this syndrome and the patient was urged to have further hematologic study including a bone marrow examination. This was done by Dr. Nathan Rosenthal and revealed a hemoglobin of 89 per cent, with 4,400,000 red blood cells per cu. mm. There was a marked leukocytosis of 22,600 per cu. mm. with a normal differential count. Examination of the bone marrow disclosed no abnormalities. There was no evidence in the blood picture of acute infectious mononucleosis; the heterophile antibody reaction was positive in a dilution of 1:64.

With the exclusion of a blood dyscrasia it became apparent that the investigation of the etiology of the hepato-splenomegaly was only beginning. Arrangements were being made to have the patient come into the hospital for observation when the course of events took a bizarre turn. Five days after the first visit to the patient one of us (F.K.) was excitedly called and informed that the patient had fainted and gone into circulatory collapse. Accordingly she was quickly transferred to the hospital. The history now obtained was that she had had a telephone conversation during which she was very much unnerved, felt faint, fell against a chair and lost consciousness. Following this she complained of weakness, dyspnea, coldness, sweating, thirst and generalized abdominal pain.

On admission the patient was conscious and oriented. Her skin was cold and clammy. There was marked pallor of the conjunctivae and mucous membrane. The tongue was dry. The blood pressure was 52 systolic and 30 diastolic. The pulse was rapid and thready. Examination of the heart and lungs disclosed no abnormalities. The abdomen was slightly distended. There was mild generalized abdominal tenderness with the maximum on the left side. There was some rebound tenderness

and rigidity in the epigastric region. The liver was palpable down to the iliac crest. The spleen was not definitely palpable. The hemoglobin was now only 64 per cent with 3,200,000 red blood cells per cu. mm. The white blood count was 10,600 per cu. mm. with a normal differential. The stool showed a slightly positive guaiac test.

It was felt that the clinical picture was that of shock due to internal hemorrhage. There was, however, no evidence of bleeding into the peritoneal cavity or into a hollow viscus. It was believed that the hemorrhage was most likely retroperitoneal and that a conservative course should be followed.

The patient was given 1,000 c.c. of blood during the night of admission. By the next morning her general condition had improved. The quality of the pulse was better and the blood pressure had risen slightly. The abdomen, however, had become slightly more distended. The liver and spleen could not be palpated. In spite of the transfusions, the hemoglobin had not risen. A surgical consultant at this time interpreted the abdominal distention as evidence of ileus, secondary to retroperitoneal bleeding. On the morning of the third hospital day it was noted that the distention

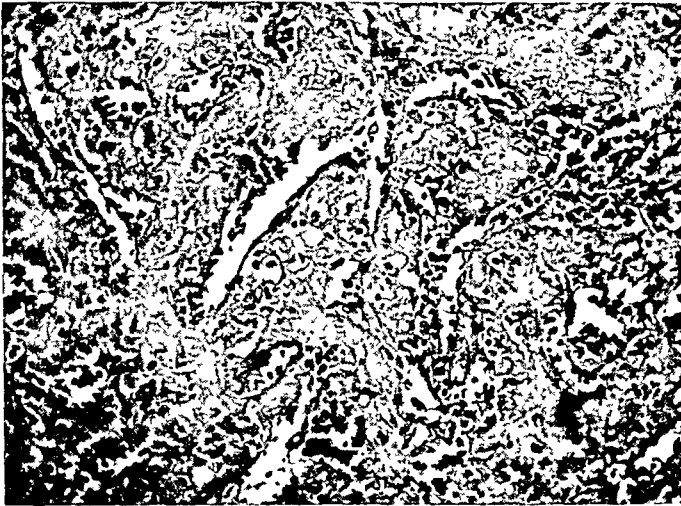


FIG. 1. Histologic section of spleen showing diffuse amyloid deposition with compression of sinusoids.

was further increased. Furthermore for the first time there was evidence of a fluid wave. Moreover, in spite of the transfusion of 2,000 c.c. of whole blood, the hemoglobin had fallen to 38 per cent. Abdominal aspiration in the left lower quadrant yielded frank non-clotting blood. It now seemed probable that the hemo-peritoneum was due to a rupture of the spleen sustained by a fall against the chair. Laparotomy with a view to splenectomy was indicated.

The exploration was performed (G.D.O.) under general anesthesia through a left upper mid rectus muscle splitting incision with a left lateral extension. The abdominal cavity was found to contain about two liters of fresh and clotted blood. It was immediately determined that the source of the bleeding was the spleen. The pedicle of this organ was clamped, hemostasis effected and the spleen quickly removed. The liver was found to be large and unusually smooth. The blood was removed from the peritoneal cavity and the abdomen closed by means of interrupted, buried, figure of eight, steel wire sutures. Penrose drainage to the tail of the pancreas was instituted. The patient continued to receive blood transfusions during and after the operation. She weathered the procedure well and made an uneventful recovery.

The spleen weighed 1,400 grams. It was encased by a large subcapsular hematoma. The capsule at one point showed a small tear. On removal of the hematoma the spleen was found to be of a reddish color and of rubbery consistence. A small tear was found in the splenic parenchyma from which the hemorrhage evidently had originated. A cross section of the spleen disclosed a diffusely homogeneous surface having a distinct waxy appearance and salmon pink color. The Malpighian follicles were entirely obliterated. Histologic section and staining reaction disclosed diffuse and marked amyloidosis (figure 1).

It was now possible to reconstruct the clinical course of events. The original sore throat had of course no relation to the illness which was accidentally discovered. Apparently this patient, having diffuse amyloidosis of the liver and spleen, had a syncopal attack and fell with her left side against a chair causing a small rupture of the spleen. This caused a subcapsular hemorrhage which gave rise to the original symptoms of shock. The subcapsular hematoma increased in size and finally caused a rent in the capsule which allowed for bleeding into the free peritoneal cavity.

We were now intent on appraising the extent of involvement with amyloid as well as investigating the etiology of this metabolic disorder. Moderate involvement with amyloid could be inferred from the Congo red test which showed 64 per cent retention. There was ample evidence of renal involvement in the presence of marked albuminuria as well as occasional granular and hyaline casts. Total blood protein was only slightly reduced to 5.0 gm. per cent, the albumin fraction being 3.2 gm. per cent and the globulin 1.8 gm. per cent. However, the kidney was able to concentrate to a specific gravity of 1.022. The blood urea nitrogen was normal. The urine did not contain amyloid casts or refractile lipoids. The intravenous pyelogram disclosed no abnormalities. There was no evidence of disturbed liver function. The cephalin flocculation test was negative. The blood cholesterol was 400 mg. per cent of which the esters were 300 per cent. There was no clinical jaundice.

An attempt to detect classical etiologic factors yielded no results. There was no history of tuberculosis contact and the roentgenogram of the chest disclosed no abnormalities. There was a vague history of a tooth infection with associated periodontal suppuration. However, a roentgen-ray of the mandible disclosed no osteomyelitis or other abnormalities. There was no clinical evidence of lues and the Wassermann reaction was negative. We were consequently in a position to assume that this patient had primary amyloidosis.

One year after operation the patient's general condition is fairly satisfactory. However, she continues to have marked albuminuria and is developing fixed hypertension (170/110), possibly due to amyloid disease of the kidneys with contraction. The liver has not changed in size.

#### COMMENT

Several provocative hypothetical considerations regarding the etiology of amyloid degeneration arise from both experimental and clinical experiences and may be pertinent. Kuczynski<sup>1</sup> was the first to produce amyloid in mice by feeding them casein-rich food, as well as by injecting such a casein preparation as nutrose. This has been repeated by others.<sup>2,3,4</sup> In conjunction with these experimental observations the clinical experiences in the Orient recorded by Snapper<sup>5</sup> would seem to be significant. Snapper points to the rarity of amyloid disease in the Orient compared to the incidence of this disease in America. Thus out of 2,046 consecutive autopsies on Chinese patients he found five cases of amyloidosis, representing an incidence of 0.25 per cent. This contrasts sharply with the experience at the Philadelphia General Hospital where out of 3,047 con-



secutive autopsies there were 50 cases of amyloidosis and at Montefiore Hospital, New York City, where out of 1,727 consecutive autopsies there were 125 instances of amyloidosis. Moreover, a comparison of incidence of amyloidosis in cases of tuberculosis, which appears to be a prominent factor in its causation, is even more impressive. Thus at the Peiping Union Medical College Hospital Snapper records only three cases of amyloid among 240 tuberculous patients. This contrasts strikingly with the reports of Rosenblatt and also of Fishberg, quoted by Snapper, which record an incidence of about 25 per cent of amyloid degeneration in autopsies on tuberculous patients. Although it is only speculation, a plausible explanation of this difference is given by Snapper which has regard for the experimental experiences mentioned before. It is pointed out that dairy products are absent from the diet of North China while these casein-rich products are partaken of abundantly in the Western world. It may be, therefore, that, especially in the presence of tuberculosis or suppuration, amyloidosis is much more likely to occur in people whose dietary habits include the ingestion of plentiful amounts of casein products.

The aforementioned facts may have some relevance to the above reported case. This patient, for the purpose of improving her health, had adopted the habit of drinking large amounts of milk and a moderate sized portion of cheese each day during the three years preceding the detection of her illness. No other etiologic or predisposing cause for amyloidosis could be discovered.

It has been observed that amyloid deposits have been spontaneously resorbed in mice. A few investigators, notably Waldenström,<sup>6</sup> have reported observations tending to show resorption of deposits in clinical cases of amyloidosis. Since the latter observations are based either on aspiration biopsies or clinical pathological tests they are not entirely conclusive. In the experience of Dr. Klemperer<sup>7</sup> no unequivocal instance of absorption of amyloid has been observed.

From the surgical viewpoint, it may be stated that rupture of an enlarged diseased spleen, as in this instance, is caused by trauma which would be insufficient to cause rupture of a normal viscus. Rupture of an amyloid spleen with hemoperitoneum, successfully treated by splenectomy, must be a rarity. It has not been encountered before at this hospital.

#### BIBLIOGRAPHY

1. KUCZYNSKI, M. H.: Neue Beiträge zur Lehre vom Amyloid, *Klin. Wchnschr.*, 1923, ii, 727-730.
2. SMETANA, H.: Experimental study of amyloid formation, *Bull. Johns Hopkins Hosp.*, 1925, xxxvii, 383-391.
3. JAFFE, R. H.: Amyloidosis produced by injections of proteins, *Arch. Path.*, 1926, i, 25-36.
4. GRAYZEL, H. G., JACOBI, M., MASLOW, H., and WARSHALL, H. B.: Experimental studies of amyloidosis, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxviii, 172-174.
5. SNAPPER, I.: Chinese lessons to western medicine, 1941, Interscience Publishers, N. Y., p. 155.
6. WALDENSTRÖM, H.: Über des Entstehen und Verschwinden des Amyloids beim Menschen. *Klin. Wchnschr.*, 1927, vi, 2235-2237.
7. KLEMPERER, P.: Personal communication.

## EDITORIAL

### *SURGICAL MEASURES FOR THE RELIEF OF INTRACTABLE ANGINAL PAIN*

ALTHOUGH the pain of coronary artery disease can usually be controlled by rest and other appropriate conservative measures, there are occasional cases in which this is impossible. Frequently recurring attacks of severe pain, coming on with the slightest exertion or even while at rest, not only are incapacitating and torturing to the victim but may constitute a grave risk to life in themselves. In such cases radical measures which offer a reasonable prospect of relief are fully justified if the operative hazard is not prohibitive and if the untoward results that may follow are not too disturbing. It is natural, therefore, that neurosurgeons have tried various operative measures in such cases.

The surgical procedures which have been employed have been designed with three primary objectives in view: to cut afferent pathways and prevent painful impulses from reaching the nervous system; to cut efferent pathways and interrupt vasoconstrictor impulses which might cause or increase spasm of the coronary vessels; and to provide a source of anastomotic circulation to supplement the inadequate blood flow through the coronaries.

The latter would be the preferable procedure if a practicable and effective method could be devised to accomplish it. The evidence at present strongly favors the view that the immediate cause of anginal pain is ischemia of the myocardium. If a significant increase in blood flow could be achieved, this might not only relieve pain but presumably also improve the nutrition and functional capacity of the myocardium. Beck<sup>1</sup> attempted to accomplish this by exposing the heart widely and suturing flaps of intercostal muscle to the myocardium. O'Shaughnessy<sup>2</sup> utilized omental grafts in a somewhat similar way. Attempts have also been made to create extensive pericardial adhesions by applying irritants to the pericardium. Thus far there is no adequate evidence that any of these measures are effective. It seems questionable indeed whether the blood flow can be notably increased in this way in a myocardium with marked and extensive sclerosis of its vessels, and at best relief would be slow as the development of a collateral circulation is a gradual process. The operative mortality reported following Beck's operation of 37.8 per cent is virtually prohibitive. The possibilities of such measures, however, have by no means been exhausted, and further study is desirable; but their use as therapeutic measures is not yet warranted.

Attempts to interrupt pain pathways stem from Jonnesco's report (1920) of four cases in which anginal pain was relieved by removal of the cervical sympathetic ganglia. This work aroused considerable interest, and during the subsequent decade a large number of similar operations were carried out,

<sup>1</sup> BECK, C. S.: Principles underlying the operative approach to the treatment of myocardial ischemia, *Ann. Surg.*, 1943, cxviii, 788-806.

<sup>2</sup> O'SHAUGHNESSY, L.: Surgical treatment of cardiac ischemia, *Lancet*, 1937, i, 185-199.

varying somewhat in detail and extensiveness. The results were not satisfactory, since even after bilateral removal of the entire cervical sympathetic chain and stellate ganglia adequate relief was obtained in only a little over half of the cases. This was at the cost of an early postoperative mortality rate of about 20 per cent.

The reason for the relative ineffectiveness of these operations was clear when more precise knowledge was obtained regarding the distribution of the afferent fibers from the heart. The principal group of fibers leave the heart in the superior, middle and inferior cardiac nerves which join the sympathetic chains on both sides in the region of the superior, middle and inferior cervical ganglia respectively. No connections have been demonstrated between these ganglia and the cervical spinal nerve roots. The afferent fibers turn back and pass down the sympathetic chain, then run through the rami communicantes to the posterior roots of the upper thoracic nerves and thence enter the cord. Excision of the stellate ganglion (formed by fusion of the inferior cervical and first thoracic sympathetic ganglia) effectively interrupts these tracts. In addition, however, there are afferent fibers passing directly from the cardiac plexus to the second, third and sometimes the fourth thoracic sympathetic ganglia and entering the cord through the corresponding posterior roots (and possibly also the fifth). These fibers are not interrupted by a complete cervical sympathetic ganglionectomy, and they provide ample means for conveying painful impulses in these cases.

These relationships are well shown by such experiments as those of White et al.<sup>3</sup> in dogs, who demonstrated that pain caused by temporary constriction of the descending branch of the left coronary artery could be abolished either by excision bilaterally of the stellate ganglia and the upper four thoracic sympathetic ganglia, or by section of the upper five thoracic posterior roots. The distribution in man seems to be quite similar to that in the dog.

Reasonably effective measures for the relief of pain date from the work of Mandle (1925) and Swetlow (1926) who reported that anginal pain was relieved by infiltration of the upper four pairs of thoracic sympathetic ganglia with alcohol. White<sup>4</sup> further perfected the technic of these injections, and he has recently<sup>5</sup> summarized the results obtained in 75 patients. In this series, good results with virtually complete relief of pain on the side or sides injected were obtained in 56 per cent and fair results with substantial reduction in severity of the pain in 21 per cent. No appreciable relief was obtained in 8 per cent, and 8 per cent died as a result of the procedure. Many of the patients were gravely ill, and the risk of an operation any more extensive would have been prohibitive.

The chief advantages of procaine-alcohol injection are that a general

<sup>3</sup> WHITE, J. C., GARREY, W. E., and ATKINS, J. A.: Cardiac innervation: Experimental and clinical studies, *Arch. Surg.*, 1933, xxvi, 765-786.

<sup>4</sup> WHITE, J. C.: Technique of paravertebral alcohol injection: Methods and safeguards in its use in the treatment of angina pectoris, *Surg., Gynec. and Obst.*, 1940, lxxi, 334-343.

<sup>5</sup> WHITE, J. C.: The surgical relief of severe angina pectoris, *Medicine*, 1948, xxvii, 1-42.

anesthetic is not required; and that if skillfully done it involves relatively little discomfort or disturbance to the patient, so that it can be carried out on patients too gravely ill to withstand an open operation. It does require a high degree of specialized skill and constant practice, and even with this about 10 per cent are failures. Serious results may follow accidental injection into the pleura or particularly the subdural space. In many of the cases there developed an intercostal neuralgia from chemical injury of the intercostal nerves which was severe in 10 per cent. This usually cleared up after a few months, but occasionally it was persistent, continuous and very distressing, and rarely it required section of the posterior nerve roots for relief.

The results are not always permanent. In 40 of White's cases there was no recurrence of pain during the period of observation (up to nine years), but pain did recur after two and one-half months to five years in 14 others. Relief from a second injection is likely to be briefer and less satisfactory. If the pain is bilateral or if it appears later in severe form on the opposite side, injections on the second side are required.

In patients who can withstand an open operation under general anesthesia, the same results can be obtained with more precision and certainty by excision of the stellate ganglion and the upper four (possibly three only) thoracic sympathetic ganglia. In this way injury to the intercostal nerves can largely be avoided as well as the occasional accidents resulting from misplacement of the needle. A second operation is required if the pain is bilateral. This operation has been used, among others, by White who has reported eight cases with one death from secondary infection.<sup>5</sup> Relief was satisfactory in all cases in which all three thoracic ganglia were removed, but there was recurrence of some pain in two, attributed to a regeneration of nerve fibers.

Lindgren and Olivecrona<sup>6</sup> have reported a series of 71 patients in whom this operation was carried out. Relief was essentially complete in 44 per cent and substantial in 41 per cent. Results were unsatisfactory in 7 per cent, and six deaths occurred within one month, three as an immediate result of the operation. No precise data are given as to the duration of the relief. In 17 of the 29 cases obtaining only partial relief, however, "migration" of pain occurred to areas previously uninvolved or in which only minor discomfort had been felt. This was usually to the opposite side of the chest, and it could be relieved by a second sympathetic ganglionectomy on that side.

In a few cases observed both by White and Olivecrona, however, the pain was felt in the neck and jaw. This was not relieved by any of the usual operative procedures. That these pains are truly anginal is shown by their appearance following exertion and by their relief by nitroglycerine. The pathways transmitting this pain are not known. It has been suggested that they may pass through possible undiscovered connections between the upper

<sup>6</sup> LINDGREN, I., and OLIVECRONA, H.: Surgical treatment of angina pectoris, Jr. *Neurosurg.*, 1947, iv, 19-39.

cervical sympathetic trunk and the cervical posterior nerve roots or (more probably) through the vagi. In one severe case, Olivecrona obtained relief by a bilateral tractotomy which produced analgesia in the distribution of the mandibular branches of both trigeminal nerves.

The most troublesome sequela was pain in the the arm lasting for one to two months, which Olivecrona attributed to a "traumatic neuritis." This was usually mild, but in some cases it was severe, in one case requiring section of the posterior nerve roots for relief.

Section of the upper four (possibly five) thoracic posterior nerve roots will also interrupt the afferent pathways from the heart. This was shown, e.g., by the animal experiments of White et al.<sup>3</sup> The operation, which requires an extensive laminectomy under general anesthesia, was regarded by them as too dangerous for such poor surgical risks. Other surgeons, however, have employed it with apparent success, notably Ray.<sup>7</sup> The great advantage is that a bilateral exposure is obtained, and the roots on both sides can be cut at a single operation.

White<sup>5</sup> collected from the literature reports of 30 cases with a mortality of 10 per cent. "Complete relief" was reported in all but one case. Olivecrona,<sup>6</sup> on the other hand, reported that the results in seven cases (with one death) were much less satisfactory than those obtained by sympathetic ganglionectomy. Some troublesome sequelae were observed, including anesthesia dolorosa in one case.

The theoretical objection that has been raised to all of these operations that they would endanger the patient by eliminating his warning signal on dangerous overexertion has not been substantiated. All observers agree that such a signal is regularly retained, either as a sense of constriction, dyspnea or dull pain which may be severe if it is referred to the neck or jaw.

Another advantage of the operations is that the sense of apprehension during an attack is usually reduced or eliminated, even if pain is not adequately relieved. In most instances, also, patients who later had fatal attacks of coronary occlusion suffered little or no pain on the side or sides which had been denervated.

Little reference has been made thus far to the part that section of the efferent (vasopressor or vasoconstrictor) fibers may play in the relief obtained by these operations, and there is great difference of opinion regarding this point. As no such efferent fibers are known to pass through the posterior roots, the relief following posterior rhizotomy presumably is due solely to eliminating the afferent pathways. Relatively little is known as to the course of the efferent fibers. There is not even agreement as to whether they come through the vagus or the sympathetics. There is at least a strong presumption, however, that some efferent pathways are interrupted by the sympathetic ganglionectomies. It has been suggested that this is the explanation for the relief obtained by a substantial minority of the patients following restricted ganglionectomies in which some afferent pathways were

<sup>7</sup> RAY, B. S.: The management of intractable pain by posterior rhizotomy, *Proc. Assoc. Res. Nerv. and Mental Dis.*, 1943, xxiii, 391-407.

not disturbed. In cases with advanced sclerosis and generally rigid arteries vasoconstriction seems relatively unimportant, but it may well be significant in those patients whose arteries still possess some resilience.

Fauteux,<sup>8</sup> on the basis of experiments with dogs, has advocated a different procedure designed to interrupt both pathways and improve the coronary circulation. This consists of a ligation of the great cardiac vein, a pericoronary artery neurectomy or both. He reported 16 cases, in most of which only a venous ligation was done, with three deaths. Relief of pain is said to have been obtained in most, and some patients were able to resume their former occupations. It is impossible at present to assess either the value or the risk of this procedure which is still distinctly experimental.

In summary, patients with even severe coronary disease withstand anesthesia and operations of this magnitude far better than might be anticipated, provided the myocardium has not suffered excessive injury from a recent infarct. At present operation is not warranted in patients whose attacks can be controlled reasonably well by conservative measures. If a competent neurosurgeon is available, patients with severe intractable angina, provided their condition is not excessively bad, can be promised an excellent prospect of substantial if not complete relief of pain by a suitable operative procedure. For patients in precarious condition paravertebral injections of procaine followed by alcohol without general anesthesia is the least hazardous, it may justifiably be tried in desperately ill patients if the need is very urgent, and it usually gives satisfactory results. With patients in better condition, open operation offers a somewhat better prospect of obtaining satisfactory relief, with less risk of untoward results. Neither ganglionectomy nor posterior rhizotomy has at yet been shown to be clearly superior to the other, although the evidence now seems slightly to favor ganglionectomy. For patients with bilateral pain, however, rhizotomy offers the big advantage that the roots can be cut bilaterally at a single operation whereas ganglionectomy is a two stage operation with an interval of at least one or two months between.

A substantial price is exacted for this relief. There is an early post-operative mortality in all these procedures of about 10 per cent, varying with the care used in selecting patients and with where the line is drawn between presumably operable and inoperable cases. In most cases temporary discomfort or pain of various types and severity follows, and occasionally this is severe and persistent.

These procedures are only palliative. There is little evidence that the function of the myocardium is significantly improved or the average duration of life materially prolonged, although this seems to have been accomplished in certain individual cases. Even this price does not seem excessive for properly selected patients with severe intractable pain, and the preliminary work with these operations seems to have reached a point which warrants their more extensive use.

P. W. C.

\* FAUTEUX, M.: Surgical treatment of angina pectoris. Experiences with ligation of the great cardiac vein and pericoronary neurectomy, *Ann. Surg.*, 1946, cxxiv, 1041-1046.

## REVIEWS

*Textbook of Endocrinology.* By HANS SELYE, M.D., Ph.D. (Prague). 914 pages; 18 × 26 cm. Acta Endocrinologica, Université de Montreal, Montreal, Canada. 1947. Price \$12.80.

In this book Selye brings together a vast amount of endocrinological data scattered through the fields of anatomy, physiology, pathology and medicine and in so doing argues for the establishment of endocrinology as a separate discipline. It is perhaps premature to justify such an attempt on pedagogical grounds, but there is no questioning its desirability as a matter of principle. As now taught in most medical schools endocrinology is presented in a series of fragments and it is left to the student to put the pieces together. How well he succeeds is a matter of opinion. It is to Selye's credit that he circumvents in one field at least the unfortunate consequences of departmentalized teaching.

The book itself is a mine of information and will well repay the time and effort of anyone interested in endocrinological matters, whether it be from the clinical or experimental point of view. The text itself is concise and always to the point and the arguments are ably presented and easy to follow. The book is perhaps too heavily weighted on the clinical side, but this is not a serious defect and the multitudinous charts, diagrams, tables and illustrations more than compensate for it. In the matter of illustrations alone the work deserves the highest praise. It is hard to see how they could be improved. The author has brought together a very impressive array of clinical photographs, practically all new, unequalled elsewhere. They will serve as a source of illustrative material for texts in all medical fields for years to come. The diagrams, too, are excellent and emphasize the trend, so apparent in the biological as well as the physical sciences, of presenting information in a graphic form. Such presentations stimulate conceptual thinking for they depend more on the use of signs and symbols than upon the written word. The reader is thus encouraged to think dynamically.

In a book which purports, according to its title, to cover the entire field of endocrinology it is unfortunate that there is such a paucity of material concerning the endocrines in plants and invertebrates, and even in the lower vertebrates. No doubt there is little here to interest the clinician, but this does not justify their dismissal in quite so casual a fashion from a text which claims to be all inclusive. Perhaps it might better have been called a textbook of mammalian endocrinology.

Certain parts of the book are highly speculative and represent the author's own views. The reader must be on his guard not to confuse fact with interpretation. The advanced student no doubt can make this distinction easily enough, but the beginner might well be led astray. The author is aware of this difficulty and warns the reader in the preface, but it is questionable whether such warnings really serve their purpose.

The absence of any detailed bibliography is explained as a matter of deliberate policy and no exception can be taken to the author's position on this point. A list of monographs and pertinent papers is found at the end of each chapter and will serve adequately to orient anyone who wishes to familiarize himself with the literature on the subject. The index is one of the book's best features and the author cannot be commended too highly for the splendid job he has done. It adds greatly to the value of the book, which is truly encyclopedic in scope, and immeasurably enhances its value to the student and the investigator. No serious student of endocrinology can afford to do without this work.

D. C. S.

*Dermatologic Clues to Internal Disease.* By HOWARD T. BEHRMAN, M.D., Assistant Clinical Professor of Dermatology, New York University College of Medicine. 165 pages; 16 × 23.5 cm. Grune and Stratton, Inc., New York. 1947. Price, \$5.00.

This book represents an interesting and new approach to the problem of cutaneous medicine. The author attempts to point out that the skin serves as a mirror to reflect evidences of the pathologic processes which may be going on in the body.

He has arranged the various diseases in alphabetical order, using in each case the simplest possible nomenclature. Each paragraph is concise and to the point. There is complete absence of any redundant material. The author has adequately illustrated his text but, unfortunately in some respects, it is apparent that the photographs have been poorly reproduced on the printed page as some of them appear too dark.

The subject matter of this text is excellent but it is to be hoped that the author may see his way clear to enlarge it and write a more complete description of each disease.

H. M. R.

*An Introduction to Physical Methods of Treatment in Psychiatry.* 2nd Ed. By WILLIAM SARGANT, M.R.C.P., D.P.M., and ELIOT SLATER, F.R.C.P., D.P.M. 215 pages; 14 × 22 cm. The Williams & Wilkins Company, Baltimore, Maryland. 1948. Price, \$3.50.

The authors are leading exponents in the application of surgical and medical technics to psychiatric problems. The methods proposed have increased in vogue partly because of demonstrated effectiveness, partly because physicians are oriented organically rather than psychologically.

The book is not intended and should not be considered an introductory text to psychiatric practice. More conservative methods have equal and frequently more sustained effect. Skill in psychotherapy remains the most essential therapeutic technic although its limited availability has encouraged recourse to physical methods. The obvious objection to physical methods, that diseases with demonstrable psychogenic etiology are to be treated organically, is countered by the authors through assumption of "inborn determinants" and organopathy which will eventually be demonstrated. Their methods have, according to the authors, "proved their worth without any theoretical justification."

Disputants will complain that the proponents of physical methods have revived unsupported speculations on inevitable and resistant constitutional factors, and that their technics are variations of organic assaults which have always been known to alter or sometimes induce personality disorder. Most psychiatrists still consider some of these methods, such as leucotomy, as experimental and even desperate. Most concede shock therapy is effective in treatment of the so-called "suicidal psychoses." Few psychotherapists place much stock in the use of drugs as anything but temporary palliatives that add to the array of tokens on which the patient becomes dependent.

The authors state emphatically that physical methods of treatment are being neglected by psychiatrists. Few psychiatrists do not accept the eclectic viewpoint of the authors, that all possible avenues of therapy are to be considered. Most would not agree that physical methods of treatment are being overlooked. The usual findings are that radical methods are abruptly applied without thorough study of the patient's problems and observations as to the effect of conservative management.

Although not personally sympathetic to some of the suggested technics or in agreement as to what can be expected from them, this reviewer knows of no other



text which attempts to justify with equal persuasion, literary style and clarity, the somatic approach to mental illness. The book inspires regret that psychopathology and psychotherapy cannot be imparted as briefly or graphically.

P. S. W.

*Procedure in Examination of the Lungs.* By ARTHUR F. KRAETZER, M.D.; revised and with a preface by JACOB SEGAL, M.D., F.A.C.P., F.C.C.P. 150 pages; 14 × 21 cm. Oxford University Press, New York. 1947. Price, \$3.50.

The present text is the third edition of this work on the fundamentals of the elements of physical diagnosis. The author in his introduction, emphasizes the importance of the induction method of learning physical diagnosis and points particularly to its value in the early diagnosis of tuberculosis. The years since the first edition of this book was written have witnessed the ascendancy of the roentgen-ray in the early diagnosis of pulmonary tuberculosis and have lessened the importance of emphasis on physical diagnosis. But the emphasis in this text is truly not on the early diagnosis of tuberculosis but on the acquiring of the art of physical diagnosis as it applies to all pulmonary diseases. This book then is unique in its value to students to guide them through the methods of developing skill in learning physical diagnosis and how to translate these findings into the diagnosis and the differential diagnosis of chest diseases.

The author employs a simple and logical method in furthering his purpose. The elements of physical diagnosis are set down: inspection, palpation, percussion, and auscultation. These elements are described as they exist in the normal chest. Then the variations from normal in fundamental pathological conditions are described. The student is encouraged always to think not of specific disease conditions but rather to gather facts found under the elements of physical diagnosis and work these facts into a diagnosis. This method is the induction method of learning and utilizes one's skill and not merely memory.

The author has a special interest in pulmonary tuberculosis and has included a chapter on the signs and diagnosis of pulmonary tuberculosis. The teaching of students is certainly deficient in the thorough understanding of tuberculosis but in the broader sense this deficiency applies to all chest disease, since physical diagnosis is the skill which is so often poorly acquired because of improper teaching methods.

An appendix has been added to include the important rôle of bronchial disease particularly in pulmonary tuberculosis. Bronchoscopy and bronchography are briefly mentioned. The growing importance of the roentgenogram is mentioned but the author reiterates his faith in the elements of physical diagnosis.

This book is certainly of value to students who are being introduced to the art of physical diagnosis. The practicing physician will upon reading this book find a fresh interest in this important subject.

M. W. J.

#### BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Arterial Hypertension.* By DAVID AYMAN, M.D., Instructor in Medicine, Tufts College Medical School, etc. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard Uni-

versity, etc. Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work; 24 × 16 cm. 1948. Oxford University Press, New York. Price, \$2.50.

*Bright's Disease.* By HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work; 24 × 16 cm. 1948. Oxford University Press, New York. Price, \$9.00.

*Clinical Laboratory Methods and Diagnosis: A Textbook on Laboratory Procedures with Their Interpretation*—4th ed. (In Three Volumes.) By R. B. H. GRADWOHL, M.D., D.Sc., F.R.S.T.M. & H. (London), Director of the Gradwohl Laboratories and Gradwohl School of Laboratory Technique, etc. Co-author (on Volume III): DR. PEDRO KOURÍ, Director, Institute of Tropical Medicine, etc. Three-volume set contains approximately 3300 pages; 26 × 18 cm. 1948. The C. V. Mosby Company, Saint Louis 3. Price, \$40.00 for three-volume set.

*Corazon Pulmonar E Insuficiencia Coronaria.* By DR. JUAN GOVEA, de la Facultad de Medicina de Paris, etc. 178 pages; 25 × 16 cm. 1948. M. V. Fresneda (Editor), Havana, Cuba. Price, \$4.00.

*The Engaged Couple Has a Right to Know (A Modern Guide to Happy Marriage).* By ABNER I. WEISMAN, M.D., Assistant Visiting Gynecologist and Obstetrician, Metropolitan Hospital, etc. Foreword by DR. ABRAHAM STONE. 256 pages; 21.5 × 14.5 cm. 1948. Renbayle House, New York. Price, \$3.00.

*A History of the Heart and the Circulation.* By FREDERICK A. WILLIUS, M.D., M.S. in Med., Senior Consultant in Cardiology, Mayo Clinic, etc., and THOMAS J. DRY, M.A., M.B., Ch.B., M.S. in Med., Consultant, Section on Cardiology, Mayo Clinic, etc. 456 pages; 24 × 15.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$8.00.

*Klinisch-Praktische Bewertung des Elektrokardiogramm-befundes.* Volume I. By PRIVATDOZENT DR. OSKAR V. ZIMMERMANN-MEINZINGEN. 227 pages; 23.5 × 15.5 cm. 1948. Verlag Wilhelm Maudrich, Wien, Germany. Price, \$8.00.

*Practical Bacteriology, Hematology, and Parasitology*—10th ed. By E. R. STITT, M.D., Ph.M., Sc.D., LL.D., Rear Admiral, Medical Corps, etc.; PAUL W. CLOUGH, M.D., Physician-in-Charge of the Diagnostic Clinic, Johns Hopkins Hospital, etc., and SARA E. BRANHAM, M.D., Ph.D., Sc.D., Senior Bacteriologist, National Institute of Health, etc. 991 pages; 23.5 × 16 cm. 1948. The Blakiston Company, Philadelphia 5. Price, \$10.00.

*Subacute Bacterial Endocarditis*—2nd ed. By EMANUEL LIBMAN, M.D., Late Consulting Physician, The Mount Sinai Hospital, New York City, and CHARLES K. FRIEDBERG, M.D., Adjunct Physician, The Mount Sinai Hospital, New York City. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work; 24 × 16 cm. 1948. Oxford University Press, New York. Price, \$3.50.

*Symposium on the Use of Isotopes in Biology and Medicine.* Contributors: HANS T. CLARKE, HAROLD C. UREY, GLENN T. SEABORG, PAUL C. AEBERSOLD, ALFRED O. NIER, CHARLES D. CORYELL, MARTIN D. KAMEN, DONALD B. MELVILLE,

DAVID B. SPRINSON, HARLAND G. WOOD, KONRAD BLOCK, DAVID M. GREENBERG, I. L. CHAIKOFF, JOSEPH G. HAMILTON, BYRON E. HALL, SAUL HERTZ, WILLIAM F. BALE, JAMES J. NICKSON, and FARRINGTON DANIELS. 445 pages;  $24 \times 16$  cm. 1948. The University of Wisconsin Press, Madison. Price, \$5.00.

*Thyroid Enlargement and Other Changes Related to the Mineral Content of Drinking Water (With a Note on Goitre Prophylaxis)*—Medical Research Council Memorandum No. 18. By MARGARET M. MURRAY, J. A. RYLE, BEATRICE W. SIMPSON and DAGMAR C. WILSON. 39 pages;  $24 \times 15.5$  cm. (paper-bound). 1948. H. M. Stationery Office, London. Price, Ninepence, net.

*The Training of a Doctor.* REPORT OF THE MEDICAL CURRICULUM COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION. 151 pages;  $24.5 \times 15.5$  cm. (stiff cardboard binding). 1948. Messrs. Butterworth & Co., Ltd., London. Price, 7s 6d., postage 9d, extra.

*Vascular Diseases in Clinical Practice.* By IRVING SHERWOOD WRIGHT, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College, etc. 514 pages;  $21 \times 14.5$  cm. 1948. Year Book Publishers, Inc., Chicago. Price, \$7.50.

*Vitamine und Vitamintherapie.* By PROF. DR. MED. EMIL ABDERHALDEN, and PROF. DR. MED. GEORGES MOURIQUAND. 408 pages;  $23 \times 15.5$  cm. (stiff paper binding). 1948. Buchhandlung und Verlag, Hans Huber, Bern. Price, 28 francs.

#### PHONOGRAPH RECORDS

*Stethoscopic Heart Records* (Revised), Set M-735 (8 sides). By GEORGE D. GECKELER, M.D. 1948. Columbia Masterworks, Columbia Records, Inc., Bridgeport, Connecticut. Price, \$8.00.

## COLLEGE NEWS NOTES

### RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949–June 30, 1950. The Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from \$2,200 to \$3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

---

### MEDICAL SPECIALTY BOARD NOTICES

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY, INC., 60 E. 66th St., New York 21, N. Y.; George M. Lewis, M.D., Secretary-Treasurer. Oral examinations will be held in Ann Arbor, Mich., October 21–23, 1948; written examinations for Group "B" candidates will be held on September 9, 1948. Closing date for applications for these examinations was August 2, 1948.

AMERICAN BOARD OF INTERNAL MEDICINE, 1 W. Main St., Madison 1, Wis.; William A. Werrell, M.D., Ass't Secretary-Treasurer. Beginning with 1949, only one written examination will be given each year. The date for the examination will be the third Monday in October of each year, and applications for admission to the examination must be filed by May 1 of that year. The requirement of an interval of a year before re-examination has been waived for candidates who failed the written examination in March, 1948, and they may take another examination in October, 1948.

The American Board of Internal Medicine customarily arranges to give the Part I (written) examination under a local proctor in both Puerto Rico and Hawaii. However, the oral examination (Part II) must be given by members of the Board, or by former members on authority from the present Board. This makes it necessary for candidates from Puerto Rico and Hawaii to come to the States for the Part II (oral) examinations.

THE AMERICAN BOARD OF PATHOLOGY, Washington University School of Medicine, St. Louis 10, Mo.; Robert A. Moore, M.D., Secretary-Treasurer. Candidates for examination in pathologic anatomy will come before the examiners on October 8, 1948, and those for clinical pathology, on October 9, 1948, at the University of Chicago. Department of Pathology.

THE AMERICAN BOARD OF PEDIATRICS, INC., 718 Royal Union Bldg., Des Moines, Lee F. Hill, M.D., Secretary-Treasurer. Oral examinations will take place at Seattle, Wash., September 10–12, 1948, and at Atlantic City, N. J., November 17–19, 1948.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC., 102 2nd Ave., S.W., Rochester, Minn.; F. J. Braceland, M.D., F.A.C.P., Secretary-Treasurer. Examinations in neurology, psychiatry, and neuropsychiatry will be given at the Langley

Porter Clinic, University of California Medical School, San Francisco, on October 11 and 12, 1948, and at the New York State Psychiatric and Neurological Institutes, New York City, on December 13, 14 and 15, 1948. Applications must reach the Secretary-Treasurer at least 90 days before the examination date.

AMERICAN BOARD OF RADIOLOGY, 102 2nd Ave., S.W., Rochester, Minn.; B. R. Kirklin, M.D., F.A.C.P., Secretary-Treasurer. Examinations will be conducted at Tampa, Fla., November 1-5, 1948, and at Atlantic City, N. J., May 31-June 4, 1949.

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA, 150 Metcalfe St., Ottawa, Ont., Can.; John E. Plunkett, M.D., F.R.C.P.(C), F.A.C.P., Honorary Secretary. Written examinations will be held in Vancouver, Edmonton, Saskatoon, Winnipeg, London, Toronto, Kingston, Montreal, Quebec City and Halifax: for Fellowship, on October 25, 26 and 27, 1948; for certification, on October 25 and 26, 1948. Oral and clinical examinations will be given at Montreal: for certification, on November 8 and 9, 1948; for Fellowship, November 15 to 23, 1948. Closing date for applications for these examinations was June 25, 1948.

---

#### POSTGRADUATE COURSES OFFERED BY OTHER INSTITUTIONS

PSYCHIATRY AND NEUROLOGY, August 30-November 19, 1948, Langley Porter Clinic, University of California Medical Center, San Francisco 22, Calif. Dr. Karl M. Bowman, Professor of Psychiatry, will direct. Fulltime course, covering general and child psychiatry, psychobiology, psychoanalysis, psychology and psychopathology, functional and organic psychoses, psychoneuroses, therapy, psychosomatic problems, neuroanatomy, clinical neurology, neuropathology, neurophysiology, electroencephalography, and x-ray diagnosis. Fee, \$200.00. Application should be made to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, at above address.

---

HEMATOLOGY AND NEUROLOGY, September 13-18, 1948, Chicago Medical Society, 30 N. Michigan Ave., Chicago 2, Ill. Classes at Thorne Hall, Northwestern University. Also CARDIOVASCULAR AND RESPIRATORY DISEASES, September 20-25, 1948. Detailed course rosters available. Fee, \$50.00 each course. Application should be made to W. O. Thompson, M.D., Chairman, Committee on Postgraduate Medical Education, above address.

---

#### MISSISSIPPI REGIONAL MEETING

A meeting of Mississippi members of the College took place in Jackson, Miss., at the Heidelberg Hotel on July 25, under the leadership of Dr. John G. Archer, F.A.C.P., College Governor for the State. The meeting began with a luncheon for members and their guests. A scientific session followed, at which papers were presented by L. T. Carl, M.D., F.A.C.P., Jackson, on "Malignant Hypertension"; by Lucian M. Ferris, M.D. (Associate), and G. H. Martin (by invitation), Vicksburg, on "The Treatment of Herpes Zoster by Autonomic Nerve Block"; and by Edgar Hull, M.D., F.A.C.P., New Orleans, College Governor for Louisiana, on "Recent Advances in the Treatment of Heart Disease."

---

#### DR. IRONS TO BE NEXT PRESIDENT OF THE AMERICAN MEDICAL ASSOCIATION

At the recent 97th Annual Session of the American Medical Association, Dr. Ernest E. Irons, F.A.C.P., of Chicago, was elected to the post of President-Elect for 1948-1949. He will succeed in 1949-1950 the newly installed President of the

Association, Roscoe L. Sensenich, M.D., F.A.C.P., of South Bend, Ind., who, in turn, succeeded Edward L. Bortz, M.D., F.A.C.P., in that position. Dr. Irons and Dr. Sensenich have both been active for many years in the work of the American Medical Association.

A Regent of the American College of Physicians and its President in 1945-1946, Dr. Irons is Professor of Medicine in the University of Illinois College of Medicine and attending Physician to the Presbyterian Hospital.

---

On the occasion of retiring as Executive Officer of the Department of Medicine of the College of Physicians and Surgeons of Columbia University, and Director of the Medical Service of The Presbyterian Hospital, Dr. Walter W. Palmer (President of the American College of Physicians, 1948-1949) has prepared an interesting report and record of the activities of the Department and Medical Service during the 26 years, 1921-1947, of his association with those institutions. It is entitled "The Department of Medicine, The Columbia-Presbyterian Medical Center, 1921-1947," and is a history of the Department and its staff during the period.

---

Grateful acknowledgment is made to Harry R. Litchfield, M.D., F.A.C.P., Brooklyn, N. Y., for his contribution to the College Library of Publications by Members of a copy of "Pediatric Progress, Therapeutics of Infancy and Childhood." Published this year by F. A. Davis Company, Philadelphia, this book is edited by Dr. Litchfield and by Leon H. Dembo, M.D., of Cleveland, Ohio.

---

The American College of Physicians takes pleasure in reporting that Philip Reichert, M.D., F.A.C.P., New York, N. Y., has become a Life Member by recent subscription.

---

Dr. Roy R. Snowden, F.A.C.P., was promoted in June from Associate Professor to Clinical Professor of Medicine in the University of Pittsburgh School of Medicine. College Governor for Western Pennsylvania, Dr. Snowden has successfully directed a number of A.C.P. Postgraduate Courses in Internal Medicine, and will this fall direct Course No. 3 which will be offered in Pittsburgh, September 20-October 2, 1948.

---

A. Carlton Ernstene, M.D., F.A.C.P., has recently been appointed as head of the Division of Medicine in the Cleveland Clinic. A graduate of the College of Medicine of the State University of Iowa, and a former member of the faculty of Harvard Medical School, Dr. Ernstene joined the Clinic staff in 1932 and has served as head of the Section on Cardiovascular Disease for many years.

---

William B. Castle, M.D., F.A.C.P., Professor of Medicine in the Harvard Medical School, and Associate Director of the Thorndike Memorial Laboratory of the Boston City Hospital, was recently appointed to succeed George R. Minot, M.D., F.A.C.P., as Director of the Laboratory. Dr. Minot has now retired also as Professor of Medicine at Harvard. He had conducted outstanding research in the two institutions for over 30 years, and was awarded a Nobel Prize in Medicine and Physiology in 1934.

Dr. Castle's distinguished investigative work has earned for him honorary degrees from Yale University and the University of Utrecht, the William Proctor, Jr., International Award for Distinguished Service in Promoting Health, the Walter Reed Medal of the American Society of Tropical Medicine, and The John Phillips Memorial Award of the American College of Physicians (1933).

At the recent meeting of the III Interamerican Cardiological Congress, Louis N. Katz, M.D., F.A.C.P., Chicago, Ill., was named Permanent Honorary President of the Interamerican Society of Cardiology.

---

Dr. Robert Clinton Page, F.A.C.P., has recently accepted appointment as Medical Director of the Arabian American Oil Company, his office being at 711 5th Ave., New York 22, N. Y. The Medical Department of the firm is responsible for an extensive program of care for approximately 25,000 employes in Saudi Arabia, where they have seven hospitals and 22 physicians. Harold H. Golz, M.D., F.A.C.P., also is a member of the Medical Department.

---

Adolph L. Sahs, M.D., F.A.C.P., has recently been promoted from Acting Head to Head of the Department of Neurology of the University of Iowa College of Medicine.

---

An honorary LL.D. degree was conferred on Thomas Sim Lee, M.D., F.A.C.P., Washington, D. C., by Mount St. Mary's College, Maryland, on June 2, 1948, in recognition "of his eminent services to Church and State and Citizenry." The citation refers to Dr. Lee's 40 years of service as a physician, to his success as a scholar and teacher at Georgetown and George Washington Universities, his inspiring public lectures, his founding of the Washington Heart Association, and to his many charitable actions. The degree was conferred on the 58th anniversary of the conferral of a similar degree by Mount St. Mary's on Dr. Lee's father, Charles Carroll Lee, M.D.

---

Philip K. Arzt (Associate), St. Paul, Minn., Assistant Clinical Professor of Neuropsychiatry in the University of Minnesota Medical School, has recently been appointed Senior Consultant in Electroencephalography to that School.

---

Joseph D. McCarthy, M.D., F.A.C.P., College Governor for Nebraska, was elected to the position of President-Elect of the Nebraska State Medical Association on May 6, 1948.

---

William C. Menninger, M.D., F.A.C.P., Topeka, Kans., President of the American Psychiatric Association, has been awarded the Chevalier of the French Legion of Honor.

---

W. Edward Chamberlain, M.D., F.A.C.P., Philadelphia, Pa., has joined a medical mission to Poland and Finland, sponsored by World Health Organization. The purpose of the mission is to bring to the Polish and Finnish people the latest advances in medical, surgical and radiological technics.

---

#### UNIVERSITY OF COLORADO INITIATES GOLD-HEADED CANE CEREMONY

Some years ago, William J. Kerr, M.D., F.A.C.P., Professor of Medicine and Chairman of the Division of Medicine of the University of California, San Francisco, instituted a ceremony in connection with commencement. In this ceremony, a distinguished physician from another school is asked to deliver an address and is presented with a gold-headed cane by Dr. Kerr. A gold-headed cane is also presented to an outstanding member of the senior class, with honorable mention given to two other senior students.

A similar ceremony was initiated this year at the commencement of the University of Colorado School of Medicine by James J. Waring, M.D., F.A.C.P., Professor of Medicine. Most fittingly, Dr. Kerr was selected to give the Baccalaureate Address and to join in making the first awards. The cane which Dr. Waring received from Dr. Kerr at the University of California in 1945 was presented to John G. Ryan, M.D., F.A.C.P., Associate Professor of Medicine in the University of Colorado, and a similar award was made to Kon Wyatt, Jr., Pueblo, Colo., who had been selected by the faculty from a list of names submitted by the graduating class. The title of Dr. Kerr's address was the "Immortality of Inspiration."

---

The American College of Radiology held a Past Presidents' Dinner in connection with its recent 25th Anniversary Meeting in Chicago. Among the past Presidents so honored were George E. Pfahler, M.D., F.A.C.P., who was the first President, and W. Edward Chamberlain, M.D., F.A.C.P., both of Philadelphia, Pa.

---

A partial list of speakers for the Annual Meeting of the Mississippi Valley Medical Society, which will be held at Springfield, Ill., on September 29 and 30 and October 1, 1948, under the Presidency of Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill., includes the following members of the College: Anton J. Carlson, M.A.C.P., Lowell T. Coggeshall, F.A.C.P., Paul S. Rhoads, F.A.C.P., and John B. Youmans, F.A.C.P., all of Chicago; Arthur R. Colwell, F.A.C.P., Evanston, Ill.; and Raymond O. Muether, F.A.C.P., St. Louis, Mo.

---

The guest speakers for the Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society include Howard T. Karsner, M.D., F.A.C.P., Cleveland, Ohio, William A. Sodeman, M.D., F.A.C.P., New Orleans, La., and Ignacio Chavez, M.D., F.A.C.P., Mexico, D. F., Professor of Medicine in the University of Mexico School of Medicine and Director of the National Institute of Cardiology of Mexico, at which institution the American College of Physicians offered a Postgraduate Course under Dr. Chavez's direction, August 2-13, 1948.

---

Colonel Otis O. Benson, Jr., (MC), USA, F.A.C.P., recently presented a paper at the Journées Médicales, in Brussels, Belgium. Colonel Benson is Chief of the Medical Research Division of the Office of The Air Surgeon in Washington, D. C.

---

Dr. George C. Griffith, F.A.C.P., Director of Postgraduate Medical Instruction in the University of Southern California, Los Angeles, is on a teaching tour of the South Pacific for the University and the U. S. Navy. He will visit Hawaii, Korea, Japan and South Pacific islands and will return during August.

---

#### NORTH DAKOTA REGIONAL MEETING, FARGO, N. D., SEPTEMBER 11, 1948

The A. C. P. Regional Meeting for members and guests in North Dakota will be held at Fargo under the Governorship of R. B. Radl, M.D., F.A.C.P., on September 11 rather than September 18 as was announced earlier. William S. Middleton, M.D., F.A.C.P., Madison, Wis., 1st Vice President, will be the guest of honor. The local chairman for this meeting is A. C. Fortney, M.D., F.A.C.P.



## OBITUARIES

## DR. LEWIS GEORGE ALLEN

Dr. Lewis G. Allen, Kansas City, Kans., died May 28, 1948, at the age of fifty-seven. He received the A.B. and M.D. degrees from the University of Kansas in 1915 and 1917, respectively. He was a Ward Surgeon in the Medical Diagnostic Service at Base Hospital No. 1, Camp Travis, in World War I. Following the war, Dr. Allen entered private practice of Radiology in Kansas City, Kans. His staff appointments were to the Bethany, Providence and St. Margaret's Hospitals, and he was Professor of Clinical Roentgenology in the University of Kansas School of Medicine.

Dr. Allen was Past President of Wyandotte County Medical Society, Councilor of the Kansas Medical Society, Past President of the Kansas City Southwest Clinical Society, and an honorary member of the Kansas City Academy of Medicine. A Chancellor of the American College of Radiology, he was Past President of the Radiological Society of North America, and the Kansas City Radiological Society. Certified by the American Board of Radiology, Dr. Allen became a Fellow of the American College of Physicians in 1943.

In addition to his teaching and medical executive offices, Dr. Allen participated in many civic enterprises. He was Chief of the Emergency Medical Service under the Civilian Defense Program for Kansas City, Kans. He was a charter member of the Kiwanis Club, and a Trustee of the Blue Cross Hospital Service. He was also a member of the Board of Directors of the Blue Shield Medical Care, of which organization he was an early and enthusiastic organizer. He was a Trustee of the Boylan Foundation for Surgical Research.

Dr. Allen has, over a long period of time, given unselfishly of his services to organized medicine, both in teaching and in the various medical societies. Through his active medical life, it was the privilege and purpose of Dr. Allen to give more than his full share to the promotion of his chosen specialty, to the preservation of physician-patient relations through prepaid medical plans, and to the reorganization of his Alma Mater to its present highly respectable position as a center of medical education.

HAROLD H. JONES, M.D., F.A.C.P.,  
Governor for Kansas

## DR. M. WILLIAM CLIFT

M. William Clift was born in Bay City, Mich., in 1883. He attended Olivet College and received his degree in medicine from the University of Michigan in 1905. During his career he served as Radiologist to the Hurley Hospital, Flint, Mich., as Consulting Radiologist to the Michigan Home and Training School, Lapeer, and to the Midland Hospital, Midland, Mich. During World War I, Dr. Clift was Chief of Laboratory Service of Base Hospital No. 36, and Officer in Charge of the School of Roentgenology in Paris.

Dr. Clift was a fellow of the American Medical Association and a member of the Michigan State Medical Society, and the Roentgen Ray Society. He was elected a Fellow of the American College of Physicians in 1920.

His death occurred on May 7, 1948.

## DR. WILLIAM DEVITT

William Devitt, M.D., was born in Philadelphia, September 18, 1874, and passed on to greater rewards on May 20, 1948, at his home in Allenwood, Pa.

Dr. Devitt received his M.D. in 1902 from Medico-Chirurgical College of Philadelphia and Sc.D. (Honorary) from Bucknell University in 1928. He was a diplomate of the American Board of Internal Medicine. He practiced internal medicine in Philadelphia from 1902 to 1914. He had one dream which he fulfilled with his own labor and time—DEVITT'S CAMP. This was established in 1912 and is said to house more than one hundred tuberculosis patients; and to it, from 1914, Dr. Devitt devoted full time as Physician in Charge. He also served as Consultant to the North Eastern Penitentiary, Lewisburg, Pa.

Dr. Devitt became a Fellow of the American College of Physicians in 1929. He was also a Fellow of the American Medical Association and a member of the Medical Society of the State of Pennsylvania, Lycoming County Medical Society, Medical Club of Philadelphia, National Tuberculosis Society, and American Academy of Tuberculosis Physicians. He was a past President of the American College of Chest Physicians and a former Director of the Pennsylvania Tuberculosis Society.

His passing will be a great loss to his friends and associates and to all those who benefited by his life work. In his memory may DEVITT'S CAMP continue aiding tuberculosis patients.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

#### DR. FRED WILLIAM GAARDE

Dr. Fred William Gaarde was born in Minden, Nebr., on June 20, 1887, and died in Rochester, Minn., on February 10, 1948. He received his S.B. degree at the University of Chicago, 1909; and his M.D. from Rush Medical College in 1912. He practiced medicine in Chicago from 1913 to 1920. From 1914 to 1918 he was instructor in medicine in the Rush Medical College and assistant on the attending staff at Presbyterian Hospital. He was an assistant to Dr. Frank Billings. He was a diplomate of the American Board of Internal Medicine. He served as a Major in the Medical Corps of the American Expeditionary Force during World War I. In 1920 he became an assistant in medicine at the Mayo Clinic and assistant professor in medicine at the Mayo Foundation of the University of Minnesota. He later became head of the General Diagnostic Section and senior consultant in the Clinic and associate professor of medicine at the Foundation. He became a Fellow of the American College of Physicians in 1929. He was also a Fellow of the American Medical Association and member of the Minnesota State Medical Association and Olmsted-Houston-Fillmore-Dodge Counties Medical Society; also of the Institute of Medicine of Chicago, the Society of Internal Medicine of Chicago, the Central Clinical Research Club, Minnesota Society of Internal Medicine, Association for the Study of Allergy, Sigma Nu, Nu Sigma Nu, and Sigma Xi. At the Mayo Clinic Dr. Gaarde was considered one of the pioneers in the investigation and treatment of allergic conditions.

WESLEY W. SPINK, M.D., F.A.C.P.,  
Acting Governor for Minnesota

#### DR. HOWARD BISHOP GARNER

Dr. Garner was born at Tyrone, Mich., October 30, 1866. He received the M.D. degree from the University of Michigan in 1892. During World War I he served in the Medical Reserve Corps of the United States Army with the rank of Captain. He practiced medicine for many years in Detroit, with offices in the David Broderick Tower. He retired from practice in 1945.

Dr. Garner was an active member of the Wayne County Medical Society, and

devoted a great deal of his time to serving on the Ethics Committee of this organization. He refused all other committee appointments. He became a Fellow of the American College of Physicians in 1922, and died on February 13, 1948.

DOUGLAS DONALD, M.D., F.A.C.P.,  
Governor for Michigan

### DR. EUGÈNE JOSEPH LEOPOLD

In the death of Dr. Eugene Leopold on January 14, the College has lost a staunch supporter. Dr. Leopold had been a Fellow of the College since 1931. He had long been active in the practice of internal medicine and the study of diabetes in Baltimore.

The son of Joseph and Rosa Leopold, Dr. Leopold was educated in the public schools of Baltimore and at Deichmann's School. He received the A.B. degree in 1901 and the M.D. degree in 1905, from Johns Hopkins University. Then followed postgraduate studies in Berlin, Munich and London from 1905 to 1907. He became an Instructor in Medicine in the Johns Hopkins University School of Medicine. He was Assistant Visiting Physician and Physician-in-Charge of the Diabetic Clinic of Johns Hopkins Hospital. He served as Visiting Physician and Chairman of the Medical Board of Sinai Hospital. During World War I Dr. Leopold served in the Medical Reserve Corps of the U. S. Army with the rank of Captain.

Dr. Leopold was a Fellow of the American Medical Association, and a member of the Medical and Chirurgical Faculty of Maryland, Southern Medical Association, Baltimore City Medical Society, American Association for the Advancement of Science, the American Tuberculosis Association, the American Association of Hospital Social Service.

WETHERBEE FORT, M.D., F.A.C.P.,  
Governor for Maryland

### DR. LEONARD GRUNER WEBER

Dr. Leonard G. Weber of New York City died in his seventieth year on November 30, 1947.

Dr. Weber was born in New York City, was a graduate of Columbia University College of Physicians and Surgeons in 1900. He served a residency in Lincoln Hospital and was associated later with the Lenox Hill Hospital and with the Manhattan Eye and Ear Hospital. Dr. Weber became a Fellow of the American College of Physicians in 1920 and was a member of the New York Athletic Club. He served in various capacities on the staff of the Lenox Hill Hospital and at the time of his death was a senior consultant in medicine at the Manhattan Eye and Ear Hospital.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. AUGUST WILLIAM FREDERICK WESTHOFF

Dr. August Westhoff, of Richmond Hill, N. Y., died on February 21, 1948. He was born in Philadelphia on August 1, 1866. He received his premedical education at New York University and received his medical degree from Bellevue Hospital Medical College in 1891. After graduation he served as pathologist at St. Catherine's Hospital, Brooklyn, from 1892 to 1913, and on the medical service at Wyckoff Heights Hospital from 1911, finally becoming Chief of the Medical Service from 1938 to 1947. He then became Director Emeritus. He was also Attending Physician at the Bethany Deaconess Hospital at the time of his death. Dr. Westhoff was a member of The

Medical Society of The State of New York and of the Medical Society of the County of Kings. A Fellow of the American Medical Association, he became a Fellow of the American College of Physicians in 1928.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. GEORGE AIKEN DOWLING

George Aiken Dowling was born at Little Valley, Minn., January 24, 1879, and died at his home in Seattle, Wash., on October 26, 1947.

He graduated from Northwestern University Medical School in 1905, and interned at Cook County Hospital, Chicago. In 1906 he visited his brother, the late Dr. Jay Thomas Dowling, in Seattle, and while there wrote the examination leading to the license to practice medicine and surgery. He then returned to Chicago to complete his postgraduate training, following which he opened his office for practice on April 1, 1907. Dr. Dowling gave most of his attention to diagnosis and internal medicine, although he enjoyed a considerable amount of general practice.

In 1919 Dr. Dowling became associated with the founders' group of the Virginia Mason Hospital and the Mason Clinic, which association continued until his retirement from practice because of ill health, in September, 1945.

From 1919 on his practice was limited to diagnosis and internal medicine. During these years his energetic interest in and wise counsel as secretary, concerning the affairs of the hospital, were invaluable during its years of growth and expansion.

Dr. Dowling was a Fellow of the American Medical Association, a member of the Washington State and King County Medical Societies, the Seattle Academy of Medicine, the North Pacific Society of Internal Medicine, and a diplomate of the American Board of Internal Medicine. He was elected to Fellowship in the American College of Physicians in 1926.

George Dowling, in addition to being a well trained and most competent and conscientious physician, was a good citizen, and never failed to give his support to all civic enterprises aimed at making Seattle a better place in which to live. He was an unusually well balanced individual. When confronted with problems, his solution was not offered until after due consideration. He was always fair in his viewpoint to an extreme degree, and was ever capable of seeing both sides of a controversy.

He will long be missed by his family, his colleagues and the profession, his many patients, and most particularly by his immediate associates at the Virginia Mason Hospital.

LESTER J. PALMER, M.D., F.A.C.P.

### DR. GRANT ORANTE FAVORITE

Dr. Grant Orante Favorite, distinguished citizen and man of medical science, was born in Ortucchio, Italy, June 20, 1903. He came to the United States of America in 1912. In 1925 he obtained his Bachelor of Science degree from Hahnemann Medical College and Hospital of Philadelphia, where he also acquired the degree of Medical Doctor in 1927. Dr. Favorite received the Master of Public Health degree from the University of Pennsylvania in 1944. A diplomate of the American Board of Pathology, Dr. Favorite was Assistant in Pathology in the Hahnemann Medical College and Hospital of Philadelphia, 1928-29, and subsequently became Instructor and Associate Professor of Pathology and Bacteriology, and Professor of Bacteriology and Head of the Department of Preventive Medicine and Public Health. In 1944 he became Associate in Bacteriology and Immunology, Jefferson Medical College of Philadelphia. Dr. Favorite was a major in the Army of the United States in 1942. Dr. Favorite was a member of the Society for Experimental Biology and Medi-

cine, American Society of Clinical Pathologists, Society of American Bacteriologists, American Association of Immunologists, American Public Health Association, Pathological Society of Philadelphia, Medical Club of Philadelphia, The Medical Society of New Jersey, Camden County Medical Society, Homeopathic Medical Societies of the County of Philadelphia and State of Pennsylvania, and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians in 1934, and a Life Member. He died May 4, 1948.

Dr. Favorite's fascinating personality, diplomatic mannerisms, and brilliant mind are a great loss to the entire medical profession.

EDWARD LEROY BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

#### DR. SAMUEL JOHNSTON

Dr. Samuel Johnston died suddenly at his home in Toronto on April 14, 1947, following a coronary occlusion at the age of 78.

Dr. Johnston was born in Ontario and received his early education in Guelph Collegiate Institute. He graduated from Trinity Medical School in 1901 and interned in the Toronto General Hospital. He early developed a special interest in anesthesiology and in 1910 went abroad for postgraduate study in this field. On his return, he devoted himself to the practice and teaching of this subject, and became Chief Anesthetist to the Toronto General Hospital. He was a past president of the American Association of Anesthetists, and first president of the Canadian Society. He was chairman of the Section of Anesthesia of the British Medical Association at the Nottingham meeting in 1926.

Dr. Johnston was a Charter Fellow of the Academy of Medicine of Toronto and was President in 1942-43. He was a member of the Rotary and Empire Clubs. In 1904 he married Dr. Margaret Macallum who survives him. He was admitted to Fellowship in the American College of Physicians in 1924.

Dr. Johnston is mourned by a host of friends, both in and out of the medical profession. Of a genial and kindly disposition he inspired a large group of students and graduates, and the foundation stone of the new edifice of Anesthesiology indelibly bears his mark.

H. K. DETWEILER, M.D., F.A.C.P.,  
Governor for Ontario

#### DR. WILLIAM MOSER

Dr. William Moser, F.A.C.P., of Brooklyn, died September 12, 1947. He was born in New York City in 1868, received his medical training at New York University Medical College and the University of Berlin. He served as pathologist and as physician at St. Catherine's Hospital, as pathologist at St. Mary's Hospital, and as physician at the Wyckoff Heights Hospital. He was elected a Fellow of the American College of Physicians in 1920.

#### DR. WESLEY H. WALLACE

Dr. Wesley H. Wallace, F.A.C.P., of Brooklyn, N. Y., died on October 14, 1947. He was born in Alexandria Bay, N. Y., November 9, 1869; received his medical degree from the Medical College of Virginia in 1899, and was formerly Instructor in Radiography at the Long Island College Hospital. He had been Attending Radiologist at the Methodist Hospital and Coney Island Hospital. He served during World War I in the Third Field Hospital Unit of the New York National Guard. He was at one time Vice President of the Radiological Society of North America and had been a Fellow of the American College of Physicians since 1920.

## DR. SAMUEL HUMES WATSON

Samuel Humes Watson was born at Vinton, Iowa, March 15, 1877. He received his medical degree from Rush Medical College in 1899. Dr. Watson served as Medical Director of the Tucson-Arizona Sanatorium from 1911-18. Other appointments which he held were: Medical Director, St. Luke's in the Desert; Physician in Chief, Barfield Sanatorium; Attending Physician, Chief of Staff, Chairman and Member of Executive Committee, St. Mary's Hospital and Sanatorium; Medical Director, Anson Rest Home for Tuberculosis. He served as former President of the Pima County, Arizona State and Arizona Anti-Tuberculosis Associations; Vice President, American Association for the Study of Allergy; Director, National Tuberculosis Association. A member of the American Sanatorium Association, and the Medical and Surgical Association of the Southwest, and a Fellow of the American Medical Association, Dr. Watson was elected a Fellow of the American College of Physicians in 1923.

Dr. Watson will long be remembered by his colleagues and his patients for his great strength of conviction and for his feeling of responsibility to his patients. Very early, and throughout his period of activity, he championed the importance of bed rest in tuberculosis. He commanded the respect of both his superiors and his subordinates. His passing will be mourned by many.

W. R. HEWITT, M.D., F.A.C.P.

## ABSTRACT OF MINUTES OF THE BOARD OF GOVERNORS

SAN FRANCISCO, CALIF.

APRIL 21, 1948

The second meeting of the Board of Governors was called to order at 1:00 p.m. on April 21, 1948, with Dr. Walter L. Palmer, Chairman, presiding, and Mr. E. R. Loveland acting as secretary. Present as guests were Dr. Hugh J. Morgan, President of the College, and Dr. A. B. Brower, a member of the Board of Regents.

Dr. Palmer read a telegram of greeting from Dr. Chauncey W. Dowden, former Chairman of the Board. The Secretary called the roll and recorded the presence of 41 governors and 15 alternates. The newly elected governors were welcomed by the Chairman.

There was considerable discussion of the immediate responsibility of the governor in the endorsement of candidates for Associateship and Fellowship in the College. Regent Brower, former Governor of Ohio, who had made a particular study of this problem, attended the meeting and spoke on the procedure developed by him and emphasized the importance of the governor getting in touch with members of the College in his area in order to ascertain their exact feeling with regard to the nominees. The governor then should summarize his study in each instance and send this to the Committee on Credentials.

Dr. Benjamin F. Wolverton, in the absence of Dr. Edgar V. Allen, Chairman of the committee appointed at the annual session in 1947 to study the method of election of governors, made the following report: "The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective states, provinces or districts which will be represented by the nominees, if elected."

"The By-Law does not specify how many or which members shall be consulted by the Nominating Committee, nor by what method. This Committee believes that each and every member should have an opportunity to express his preference for Governor. It also believes that this expression or preference by all members of a given state or constituency should merely serve as a guide for the Nominating Committee, and should not be binding on the Committee to nominate the member receiving the most votes. It is conceivable that, in some instances, the member receiving the most votes would not be a desirable Governor.

"In view of these and many other considerations which have been discussed by the Committee, we offer the following plan and recommend its adoption:

"Each year, when the candidate lists are mailed to the membership, those going to the state or constituencies whose Governor's terms are about to expire shall be accompanied by a suitable form on which the members may state their preference for Governor. On the return of these forms to the office of the Executive Secretary, the names offered and the number of votes for each shall be listed and given to the Nominating Committee, to be taken into consideration in making its nominations."

The adoption of the report was moved by Dr. Wolverton and seconded by Dr. Asa L. Lincoln. After extensive and lively discussion Dr. Wallace M. Yater moved as an amendment to the resolution a suggestion made by Dr. Flinn that the new governor be elected one year in advance in order that he might serve as "Governor-Elect" and thereby be enabled to learn from the retiring governor some of the details. Dr. Flinn seconded the amendment.

Mr. Loveland presented a detailed statement of the functioning of the Nominating Committee, emphasizing the fact that serious study is made of each situation and an effort made to obtain the man best fitted for the position rather than the most popular one.

Dr. Donald moved a second amendment to the resolution suggesting that the Nominating Committee be requested to send to the Fellows in the district in which the new governor is to be elected the names of three to five individuals with the request that they indicate their preference. The results of this policy would serve to guide the Committee. The amendment was seconded by Dr. Yater. The amendment was put to a vote and lost, there being 8 in favor and 32 opposed. Dr. Yater's amendment for the election of Governors one year in advance of their taking office was put to a vote and was lost.

The original resolution was put to a vote and lost, the vote being 10 in favor and 32 opposed.

Dr. Cason nominated Dr. Robert Wilson, Jr., from South Carolina to succeed Dr. J. Edwin Wood, Jr., resigned, as a member of the Committee on Credentials. Dr. Yater moved that the nominations be closed. Dr. Flinn seconded the nomination, and the vote was unanimous.

Mr. Loveland distributed copies of the financial reports of the College for the past year and gave a brief analysis.

In behalf of the Credentials Committee Dr. Yater made the following statement: "There are two entirely different items to be considered:

"(1) The Committee realizes that the number of applicants for admission is growing steadily. The question comes up from time to time about a candidate who is not an internist, but is a neuropsychiatrist, a dermatologist, or some other affiliated specialist. The informative booklet of the College says that membership need not be made up only of internists, but may include those properly qualified in pediatrics, neurology, psychiatry, public health, radiology, and so forth.

"The Committee believes it would be well seriously to consider changing our regulations and limiting membership in this organization to those who are internists and to discontinue after a certain time to take in men who are not internists, even though they be engaged in affiliated specialties.

"The Committee makes this recommendation primarily to further limit the size of the College. These affiliated specialties all have their own certifying boards and their own special societies, and the Committee questions whether radiologists, dermatologists, and a few others, ever take a very vital interest in the College. They are amiable and distinguished people who are in purely scientific branches, a little different from strict internal medicine."

Upon motion by Dr. Yater and seconded by Dr. R. R. Snowden, it was moved that this recommendation be approved and recommended for adoption to the Board of Regents, and the matter was opened for discussion. After protracted discussion the motion was put to a vote and lost, there being 10 in favor and 34 opposed.

Dr. Yater then presented the second part of the recommendations of the Credentials Committee as follows:

"(2) In spite of explanatory and clear definitions which the Survey Committee made and were incorporated as amendments to our By-Laws last year, it is still a very difficult matter from data available to come to a conclusion as to who is an internist, and whether he is a man who will ultimately be able to attain certification. Even those members of the Credentials Committee who were most violent in their opposition to the recommendations some of us made, namely, that before a man should be considered as an Associate he should be certified by the American Board of Internal Medicine, have come to the conclusion that such a rule wouldn't be too objectionable, after all, if we could limit the membership of the College to those who are internists. If we decide to take only internists, we can only recognize those who have already been certified, and many difficulties would be solved and hours of debate would be eliminated. The Committee feels that it would make for a much stronger and more homogeneous organization."



Dr. Yater moved and Dr. Alex. M. Burgess seconded the adoption of this recommendation. After spirited discussion the motion was put to a vote and lost, there being 10 in favor and 30 opposed.

Dr. Cason made the following motion:

"(1) That we recommend to the Board of Regents that a committee be appointed to study the question of the approach to accepting Associates;

"(2) to study the advisability of extending the number of years of Associateship;

"(3) to study any method that may be devised by which the standards required to become a Fellow can be raised through which the size of the College may be properly limited;

"(4) to consider the question of eliminating Associateship.' That is just to be considered and this committee ought to be empowered to make a careful and complete study. If it takes the committee two years to bring in a report, all right, but it should make a comprehensive study of what our ills are and what we need to do."

The motion was seconded by Dr. Yater and, after some discussion, was carried unanimously.

Dr. Burgess, in order to obtain an expression of opinion on the part of the Governors, moved that it is the present sentiment of the Board of Governors, that the Associateship should eventually be eliminated. The Chairman ruled that this was a request for an expression of sentiment. Twenty-seven hands favored the suggestion and 14 opposed it.

Mr. Loveland discussed with the Governors the proposed sites for the 1949 and 1950 meetings.

In closing the Chairman expressed his regret that several governors who had given the College a long and distinguished service could no longer qualify for reelection, as a result of the introduction of the regulation limiting the term of governors. In behalf of the Board he expressed great appreciation to these men: Dr. Flinn of Delaware, Dr. Cason of Florida, Dr. Levy of Texas, Dr. Hitchcock of Montana, Dr. Holmes of Arizona, Dr. Giddings of Georgia, Dr. Dowden of Kentucky, Dr. Drake of Maine, Dr. Suarez of Puerto Rico. A rising vote of appreciation was given to the retiring members and the meeting adjourned at 3:10.

WALTER L. PALMER, *Chairman,*  
*Board of Governors*  
E. R. LOVELAND, *Secretary*

# ANNALS OF INTERNAL MEDICINE

VOLUME 29

SEPTEMBER, 1948

NUMBER 3

## THE ALARM REACTION AND THE DISEASES OF ADAPTATION \*

By HANS SELYE, M.D., Ph.D., D.Sc., F.R.S.(C), *Montreal, Canada*

IN a lecture such as this it would be impossible to review the rather voluminous literature on the adaptation syndrome and the diseases of adaptation, but this is hardly necessary in any case because several extensive surveys of this field have been published in recent years (Albright, 1942-43; Albright, 1943; De La Balze, 1946; Cannon, 1932; Crile and Lower, 1915; Ingle, 1942; Laflaquière, 1942; Leblond, 1939; Maitre, 1942; Overbeek, 1947; Selye, 1940; Selye, 1941; Selye, 1944; Selye, 1946; Sundstroem and Michaels, 1942; Tepperman, Engel and Long, 1943; Varangot, 1940).

Since apparently one of the most important diseases of adaptation is hypertensive disease—especially the so-called “renal hypertension”—it would be well to discuss the pertinent literature, but here again the limitations of space force me merely to refer the reader to the most useful relevant reviews (Braun-Menendez, Fasciolo, Leloir, Munoz and Taquini, 1943; Braun-Menendez, Fasciolo, Leloir, Munoz and Taquini, 1946; Carrière and Huriez, 1936; Dumont, 1946; Fishberg, 1939; Gallaverdin, 1920; Goldring and Chasis, 1944; Goldring et al., 1946; Hueper, 1944-45; Lichtwitz, 1942; Page and Corcoran, 1945; Trueta, 1947; Viersma, 1946) and particularly to a synopsis of this field which I recently gave in my textbook (Selye, 1947). Here I should merely like to summarize the concept of the Diseases of Adaptation and to survey especially the more recent observations which support it. Perhaps it will help to follow a concise description of pertinent observations if we first outline the theories which we intend to illustrate with them. It must be stated at the onset that certain links in the chain of events which we believe to be responsible for the Diseases of Adaptation have not yet been fully proved and others may have to be replaced in the future, but wherever uncertainty exists, we shall emphasize the gaps in our knowledge.

\* The essence of this paper was presented before the American College of Physicians at the 29th Annual Session in San Francisco, April 19, 1948.

# I. SUMMARY OF THE GENERAL-ADAPTATION-SYNDROME CONCEPT

The pertinent observations made up to the present time are most readily compatible with the following interpretation:

Under the influence of systemic stress, occasioned by a variety of specific damaging agents, the organism responds with a *general-adaptation-syndrome* whose manifestations are essentially independent of the specific nature of the exposure. The syndrome evolves in three distinct stages: (1) the *alarm reaction*, (2) the *stage of resistance* and (3) the *stage of exhaustion*. Since hypertension is essentially a disease of the stage of resistance, it will not be necessary to insist upon the other two phases here.

It is thought that at least certain types of spontaneous hypertension in man are due to excessive exposure to *stress* or to derangements in the normal defense reaction against stress. A variety of stresses elicit metabolic changes—the so-called “catabolic impulse” (see below)—which are particularly prominent during the “shock phase” of the alarm reaction, but many of them remain detectable throughout the entire general-adaptation-syndrome.

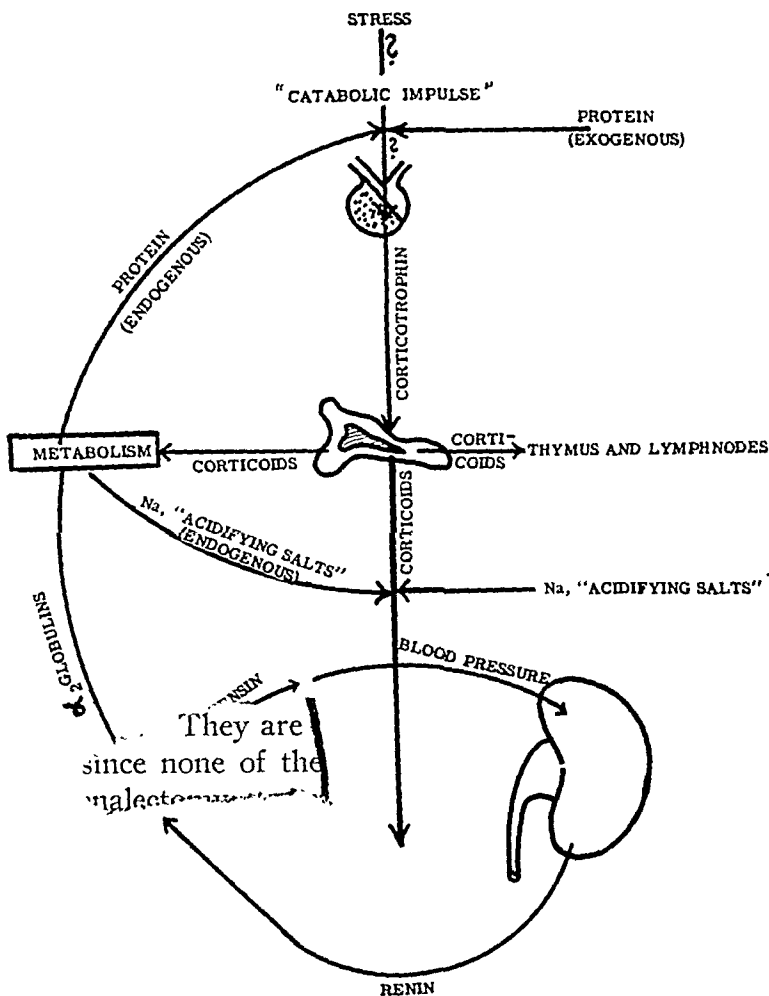
Apparently this “catabolic impulse” in its turn influences the *anterior-lobe* to produce an excessive amount of corticotrophin. Corticotrophin causes increased corticoid production by the *adrenal*. The corticoids produce involution of the *thymus* and *lymph nodes* as well as certain *metabolic changes*, for instance: retention of sodium, gluconeogenesis from protein and production by the liver of  $\alpha_2$ -globulin (that is, hypertensinogen). Directly or indirectly through their metabolic action, the corticoids also cause a *renal-type of hypertension* with nephrosclerosis. It has not yet been clearly established whether corticoids act first on the kidney and, through the renal-pressor mechanism, secondarily cause hypertension or whether they primarily raise the blood pressure and produce nephrosclerosis as a result of the hypertension. These interrelations are summarized in the graph which also comprises some additional data to be discussed below.

Obviously during stress *sympathetic stimulation*, liberation of *adrenalin* and perhaps even a discharge of pituitary *vasopressin* may likewise contribute to raise the blood pressure, but these effects are rather evanescent and will not be discussed today. They are of importance mainly during acute stresses of short duration.

## II. OBSERVATIONS UPON WHICH THE ABOVE CONCEPT IS BASED

Let us now discuss the most important observations which led to the formulation of the above concept.

*Stress*. It was found that many otherwise entirely dissimilar non-specific damaging agents produce a “catabolic impulse” mainly characterized



by a breakdown of body proteins and an increase in the concentration of protein catabolites and proteolytic enzymes in the blood. This is accompanied by loss of weight and by histologic evidence of a generalized breakdown of cells. At the same time stress elicits a typical alarm reaction with the characteristic adrenal-cortical enlargement, gastrointestinal ulcers, involution of lymphatic organs, etc. Prolonged stress causes less marked catabolic reactions but concomitantly with the adrenal cortical enlargement it can produce nephrosclerosis and hypertension, especially in animals sensitized by unilateral nephrectomy and high-sodium, high-protein diets. The adrenal enlargement is manifestly due to increased corticotrophin production, but it is not quite clear through what pathways stress acts upon the anterior-lobe.

Sayers and Sayers (1947) believe that stress increases the consumption or utilization of corticoid hormones by tissues and that the resulting decrease in their blood-level causes a discharge of corticotrophin by the pituitary

and is thus responsible for the cortical enlargement characteristic of stress reactions. There is no doubt that excessive amounts of corticoids can cause "compensatory atrophy" while partial ablation of the adrenal cortex produces "compensatory hypertrophy" of adrenal cortical tissue because an excess of corticoids tends to depress, while a lack of cortical hormones increases, corticotrophin production by the anterior-lobe under near-physiologic conditions.

Our observations lead us to believe, however, that it is precisely during times of excessive stress that this hormonal self-regulation breaks down. Manifestly the large amounts of urinary corticoids observed during the alarm reaction in human beings (Venning and Browne, 1945; Venning and Kazmin, 1946) indicate that far from there being a lack there is actually an excessive production of corticoids during stress and this hypercorticoidism is sufficiently severe to result in the "spill" of active corticoids into the urine.

Experiments which we performed in collaboration with Misses Stone and Martin showed that the stress of exposure to cold leads to enlargement of the adrenal cortex even in rats which were so severely overdosed with desoxycorticosterone acetate (DCA) that they were anesthetized by it throughout the experiment (intraperitoneal administration of up to 12 mg./100 gm. body weight/day). At the same time the adrenals of these rats discharged their lipid granules in a manner characteristic of corticotrophin action (judged by frozen sections) <sup>is turn influenced by</sup> corticotrophin. Corticoid III and by the brown appearance of the glands upon naked eye examination.

Subsequently Mr. Moya of our Institute determined the ascorbic-acid content of the adrenals in rats exposed to cold while under DCA anesthesia. Here again the depletion in adrenal ascorbic-acid, characteristic of corticotrophin action, was demonstrable irrespective of the DCA overdosage. Indeed the damaging effect of DCA intoxication in itself (without exposure to cold) sufficed to cause rapid loss of adrenal ascorbic-acid when the resulting anesthesia was sufficiently profound. Perhaps the reason why Sayers and Sayers (1947) were able to inhibit the loss of adrenal ascorbic-acid by DCA and other corticoids is that they used lesser degrees of stress; as we have said above at near-physiologic levels corticotrophin production is undoubtedly dependent upon the corticoid concentration in the blood.

There are many similar hormonal homeostatic mechanisms which illustrate that the maintenance of important physiologic functions is assured by several alternative regulators. Thus at near-physiologic dose levels, a discharge of insulin tends to decrease the fasting blood sugar but this is counteracted by adrenaline secretion. Indeed there is a direct proportionality between the amounts of insulin and adrenaline which must be simultaneously supplied to assure the maintenance of the glycemic level in the presence of an excess of one of these hormones. However, if excessive doses of insulin are administered, no dose of adrenaline can prevent hypoglycemia. There is no reason to believe that stress actually causes "consumption" of corticoids, but it certainly raises corticoid requirements and thus results in a "relative cortical insufficiency."

At near-physiologic dose levels corticotrophin production—and the resulting adrenal cortical enlargement and activity—depend upon the degree of stress and can be inhibited by exogenous corticoids. Within these limits, the dose of corticoids required to accomplish this is proportionate to the degree of stress. In the event of excessive stress, however, this mechanism becomes comparatively unimportant and other (hitherto not clarified) mechanisms are called upon to augment corticotrophin activity.

*The "Catabolic Impulse."* As previously stated, stress elicits a catabolic impulse. This is characterized grossly by loss of weight, histologically by death of cells in various organs and biochemically by an increase in the blood concentration of proteolytic enzymes (e.g., fibrinolysin) and protein breakdown products (amino-acids, polypeptides, peptones, uric acid and other N.P.N. constituents). The concomitant hyperkalemia is presumably also due to tissue breakdown. At the same time there may be a rise in the blood concentration of histamine or "H-substance"-like compounds, hypochloremia, hypothermia, a decrease in blood pressure and multiple gastrointestinal ulcers with hemorrhages into the intestinal tract. All these manifestations are especially prominent during the early "shock-phase" of the alarm reaction but may remain manifest to some extent throughout the entire general-adaptation-syndrome. They are not mediated through pituitary, adrenal or renal hormones since none of these manifestations are prevented by hypophysectomy, adrenalectomy or nephrectomy; indeed most of these changes are even more pronounced in hypophysectomized, adrenalectomized or nephrectomized animals because in them stress-resistance is diminished. It is not yet known through what mechanism stress affects corticotrophin production, but the facts established up to the present time are compatible with the view that any, or all, of the catabolic blood-chemical changes may increase corticotrophin production during stress. We know that the nervous stimuli which reach the pituitary directly from the hypothalamus are not indispensable since stress causes adrenal cortical enlargement even after section of the pituitary stalk; it is not impossible, however, that other (e.g., periarterial) nervous pathways may act directly upon the pituitary, and it is certain that nervous (and even purely emotional) stress can cause adrenal cortical enlargement and typical alarm-reaction changes as shown by animal experiments. Perhaps here the nervous stimuli increase corticotrophin production through the intermediary of some blood borne metabolites.

*The Hypophysis.* *Hypophysectomy* prevents the production of nephrosclerosis and hypertension by stress, and in the absence of the pituitary more than the mere maintenance dose of hypophyseal extract is necessary to withstand stress. This implies that increased hypophyseal activity (presumably corticotrophin secretion) is essential for resistance to stress and that conversely if such an increased pituitary hormone production is prevented by hypophysectomy, stress no longer affects the adrenal, kidney, blood pressure and the thymico-lymphatic apparatus, hence these appear to be lower links in the chain-of-events than the hypophysis.

*Hypophyseal extracts* rich in corticotrophin cause adrenal cortical enlargement, nephrosclerosis, hypertension and thymico-lymphatic involution in intact animals but exert none of these effects after adrenalectomy. Hence, presumably the pituitary hormones influence these targets through the intermediary of the adrenal cortex and natural (endogenous) corticoids can produce renal lesions and hypertension.

*The Adrenals.* As previously stated *adrenalectomy* prevents the involution of the thymus and lymphatic organs which is normally produced either by stress or by anterior-lobe extracts. It also prevents the production of hypertension and nephrosclerosis by anterior-lobe extracts, but technical difficulties make it impossible to establish whether stress could produce these latter changes in adrenalectomized animals since following ablation of the supra-renal stress-resistance becomes too poor to withstand pertinent experiments. Significantly, more than the maintenance dose of corticoids must be administered to adrenalectomized animals if they are to withstand stress. Hence, presumably increased cortical function is an essential part of the defense reaction against stress.

High doses of *mineralo-corticoids*, such as DCA, produce hypertension, nephrosclerosis and involution of the thymico-lymphatic apparatus, irrespective of whether the pituitary or the adrenals have been removed or not. Presumably excessive amounts of corticoids, such as are produced during the general-adaptation-syndrome, can elicit nephrosclerosis and hypertension.

*Thymus and Lymphatic Organs.* As previously stated, the characteristic involution of the thymico-lymphatic apparatus, seen during the general-adaptation-syndrome, is elicited by a variety of *stresses*, but only in the presence of both anterior-lobe and adrenals. *Hypophyseal extracts* can cause such involution even in hypophysectomized animals (and in the absence of stress), but only in the presence of the adrenals; *corticoids* act in this manner in either hypophysectomized or adrenalectomized animals (and in the absence of stress).

Only direct application of radium or *roentgen-rays* to the thymus region or injection with *folliculoids* and *mustards* has been shown to cause thymico-lymphatic involution in adrenalectomized animals. Presumably these agents have a direct effect upon the lymphatic elements, while all other types of stress, so far examined, act through the anterior-lobe—adrenal-cortex mechanism. It has been claimed that  $\gamma$ -globulins, liberated from the bodies of thymocytes, play an important rôle in serologic defense reactions during stress, but this has not been unanimously confirmed.

*The Kidney.* The rôle of the kidney in hypertension has been discussed by various authors (see reviews cited in introduction). Suffice it here to examine its participation in the hypertension resulting from exposure to stress.

Manifestly, the hypotension characteristic of the "shock-phase" may so decrease the blood pressure, and hence the blood supply of the kidneys, that renin production is increased as it is after the Goldblatt clamp. Our

experiments have shown, furthermore, that the nephrosclerosis induced by DCA causes hyalinization of individual glomeruli and thus diminishes their blood supply at the time hypertension develops as a result of corticoid over-dosage.

Recent experiments with the "*endocrine kidney*" are also relevant (Selye and Stone, 1946). The "*endocrine kidney*" is prepared by decreasing the renal blood pressure to the level of the colloid-osmotic pressure of blood; under these conditions filtration and urine production cease, while the renal tissue remains sufficiently well supplied with blood to live and to produce hypertensive substances. As far as urine production is concerned, the bearer of an endocrine kidney is exactly equivalent to a unilaterally nephrectomized animal, but unlike the latter it develops marked hypertension and nephrosclerosis in the contralateral, though never in the purely "*endocrine*," kidney. It appears possible therefore that under the influence of DCA certain individual nephrons, whose glomeruli are severely hyalinized, become transformed into individual "*endocrine-nephrons*." In these transformed units pressor substance production is apparently increased in essentially the same manner as after the "*endocrine kidney*" operation and hypertension ensues.

Perhaps stress acts upon the blood pressure by increasing first corticotrophin, then corticoid hormone production and through the latter the elaboration of vasopressor substance in individual "*endocrine-nephrons*."

It may incidentally be mentioned that with the endocrine kidney technic it was possible to demonstrate the following facts:

1. Urine secretion is not essential for the maintenance and endocrine function of renal parenchyma.

2. The renotrophic action of certain steroids (e.g., testosterone) is independent of urine secretion, since it is manifest in the "*endocrine kidney*." It cannot therefore be regarded as a "work hypertrophy" secondary to metabolic processes which necessitate the formation of urine with special characteristics.

3. The "*juxtaglomerular apparatus*" is not essential for the production of renal hypertension since in the endocrine kidneys of many animals this region completely disappeared (together with most of the glomeruli), yet the blood pressure rose.

4. Irrespective of urine formation the endocrine activity of the kidney suffices to produce lesions similar to those elicited with DCA.

5. Unlike the cardiovascular damage caused by stress, anterior-pituitary preparations or DCA, that elicited by the "*endocrine kidney*" is uninfluenced by dietary sodium or protein.

6. Recent experiments which we performed in collaboration with Dr. C. Schaffenburg revealed that rats bearing an "*endocrine kidney*" develop hypochloremia similar to that caused by DCA, but without any accompanying hypokalemia. This gives further support to our previously expressed



view that the hypokalemia of DCA overdosage is not an important etiologic factor in the production of nephrosclerosis and hypertension by this hormone.

7. Careful histologic study of the endocrine kidney showed that active proliferation with the appearance of numerous mitoses, enlarged cells with polymorph atypical nuclei, loss of eosinophile granules and loss of the brush border, occur especially in the inner zone of the medulla, that is to say where the renal tissue consists mainly of the distal portions of the proximal convoluted tubules. It is rather surprising that a decrease in the blood supply to the renal parenchyma should cause such marked proliferative changes in one specific region while all other parts of the kidney undergo involution and atrophy. Naturally the possibility comes to mind that this zone may be the source of the renal pressor-substances, but at the moment such an interpretation is difficult to prove with certainty.

Trueta (1947) has clearly demonstrated that a decrease in blood pressure—while diminishing blood flow through the renal cortex—augments the circulation through the juxtamedullary zone of the kidney; since it is precisely here that proliferative processes are seen in the endocrine kidney, the question arises whether this growth stimulus could not result from an increased blood supply to this particular zone.

The fact that mitotic proliferation, loss of eosinophile granules, loss of the brush border and proliferation into the lumen with a massive transformation of proximal tubules into solid cords may be the morphologic substrate of renal pressor material, is further supported by an examination of numerous kidneys from patients who died of malignant hypertension and in whom I have seen similar changes although limited to a certain number of nephrons only.

It is not possible with the endocrine kidney technic to answer the important question whether hypertension or nephrosclerosis is the first event to initiate the well known "vicious circle" which develops in animals in which chronic renal hypertension has been produced by various means. In our experiments nephrosclerosis in the contralateral kidney and the rise in arterial pressure developed almost simultaneously. It is for this reason that in the above schematic drawing we do not indicate clearly how the corticoids affect the renal pressor mechanism.

Our experiments do not show that the nephrosclerosis seen during the general-adaptation-syndrome produces hypertension through the renin-hypertension mechanism; it is equally possible that pressor amines or other pressor renal substances are involved. We feel, however, that the bulk of evidence presented by other laboratories is in favor of the renin theory.

### III. FACTORS INFLUENCING THE HORMONAL DEFENSE MECHANISM

*Kind of Stress.* Earlier work showed that almost any type of systemic damage or stress causes essentially the same alarm-reaction symptoms. It is noteworthy, however, that upon prolonged exposure to stress,

diseases of adaptation (e.g., hypertension and nephrosclerosis) are not invariably produced. In our experiments, exposure to cold proved to be especially conducive to nephrosclerosis, while forced muscular exercise, subcutaneous injection of formaldehyde and other types of stress were less effective in this respect. This is in agreement with the clinical observation that not any type of chronic stress and strain will necessarily lead to nephrosclerosis and hypertension. Indeed, most chronic diseases (e.g., tuberculosis, syphilis, malnutrition) do not have such an effect. Yet, if the mechanism through which stress produces nephrosclerosis and hypertension is the liberation of mineralo-corticoids, it is difficult, at first sight, to understand why the results of stress are not invariably the same. The excess production of corticoids is a non-specific effect of stress, but perhaps the "catabolic impulse" is more dependent upon the specific nature of the damaging agents and intermediate metabolism plays a most important rôle in determining whether the excess mineralo-corticoid material produced results in nephrosclerosis and hypertension.

As we shall see below, even the high doses of anterior-pituitary extracts or DCA are not, in themselves, conducive to nephrosclerosis and hypertension, except after special sensitization (e.g., by diet rich in sodium and protein, partial nephrectomy). Perhaps the specific metabolic effects of stress may similarly sensitize or desensitize the organism to excess mineralo-corticoids owing to changes in intermediate metabolism which imitate the derangements produced by the sensitizing or desensitizing diets.

It has been shown that the kidney-damaging action of nephrotoxic sera is increased by simultaneous administration of DCA (Knowlton et al., 1946), and the possibility should be kept in mind that damaging agents produce the changes characteristic of the various "diseases of adaptation" through a dual mechanism; one factor is non-specific (independent of the type of agent and merely dependent upon the degree of damage)—this would be the excess production of corticoids; the other factor is largely specific, and it determines why certain infections, allergies, intoxications and other types of exposure exert a preferential, selective action upon the kidney, the joints, the cardiovascular system, etc.

*Diet.* Our earlier experiments concerning the sensitization of experimental animals to the nephrosclerosis-producing effect of stress, hypophyseal extracts and DCA have since received ample confirmation. It is now clear that excess sodium, and not chloride, is responsible for this effect of NaCl, since numerous other salts of Na exert a similar effect, while other chlorides are ineffective. It may be added that it is not merely the basic nature of the Na that counts since the salts of other strong bases (e.g., KCl,  $\text{NH}_4\text{Cl}$ ) are ineffective. Indeed, excess administration of ammonium chloride, ammonium nitrate, calcium chloride and other "acidifying salts" counteracts the sensitizing effects of sodium and inhibits the production of nephrosclerosis by stress, hypophyseal extracts or DCA.

Recent experiments performed in collaboration with Drs. Hay and Prado showed, furthermore, that protein-rich diets sensitize the organism to the adrenal-cortex-enlarging effect of stress and to the nephrosclerosis-producing and hypertensive actions of anterior-lobe extracts. Curiously, protein-rich diets have no significant effect upon the production of nephrosclerosis and hypertension with pure corticotrophin, DCA or the "endocrine kidney."

More recently we tried to analyze the mechanism through which high-protein diets exert this effect. It was shown that while on synthetic diets containing 30 per cent casein, lyophilized anterior-pituitary material (LAP) regularly causes nephrosclerosis in rats sensitized by unilateral nephrectomy and a high sodium intake, no nephrosclerosis or hypertension occurs if 15 per cent of the dietary protein is substituted by starch.

It is actually the decrease in protein and not the increase in starch that counts, since if the excess starch in a 15 per cent casein diet is substituted by a calorically equivalent amount of fat, nephrosclerosis and the other manifestations of hypertensive disease still fail to occur.

Various protein preparations differ in their ability to cause kidney damage; casein, egg albumin and wheat gluten are more damaging for instance than lactalbumin, gelatin or zein. It would be important to determine whether the effect of certain proteins is due to their content in specific amino-acids or poly-peptides, but among the many amino-acids and amino-acid mixtures which we have examined, none equalled casein in its ability to increase sensitivity to the toxic effects of LAP. However, protein-hydrolyzates and amino-acid mixtures were also effective.

Since protein-rich diets do not significantly augment the nephrosclerotic effect of pure corticotrophin or DCA, it is probable that most, if not all, their effects are due to an increase in the ability of the organism to produce corticotrophin when the requirements for this hormone are high (e.g., stress or LAP). Perhaps this modification of the cortical response is not merely quantitative but even qualitative, inasmuch as protein-rich diets may especially stimulate the production of those corticoids which are particularly active in producing nephrosclerosis and hypertension.

An unpublished experiment of my colleague Dr. Prado is noteworthy in this connection. He found that following unilateral adrenalectomy the compensatory hypertrophy of the remaining adrenal is augmented by high-protein diets, in the same manner as the corticotrophic effect of stress (e.g., cold). It is not yet entirely clear whether the protein-rich diets synergize the action of corticotrophin or whether they increase the endogenous production of the latter when an animal is exposed to stress. This question can only be solved by experiments on hypophysectomized animals injected with a given quantity of corticotrophin, and such experiments are now under way in our Institute. In any case, high protein diets in themselves do not significantly stimulate the adrenal-cortex. Their action becomes manifest only under stress or after partial adrenalectomy, that is at times when corticotrophin production is above normal. This may clarify certain apparent

contradictions in the literature on the effect of dietary protein upon adrenal structure. Perhaps if the diet is in itself damaging and thus increases corticotrophin production, then a high protein concentration is conducive to an excessive cortical stimulation, but such is not the case if the animals are in perfect condition.

Our preliminary observations suggest that perhaps, under the influence of systemic stress, some inactive precursor or activator (enzyme?) normally present in anterior-lobe cells is brought in contact with protein catabolites (substrate?) and that active corticotrophin results from this interaction.

The following simplified table may help to summarize our observations concerning the principal factors influencing the hormonal production of nephrosclerosis and hypertension.

TABLE I

Factors Influencing the Production of Nephrosclerosis and Hypertension by Stress, Hypophyseal Extract (LAP), Desoxycorticosterone Acetate (DCA) or the "Endocrine Kidney"  
(↑ = increase; ↓ = decrease; + = action present; 0 = no action;  
? = pertinent experiments suggestive, but, due to high mortality inconclusive)

Hypertensive agent	Na ↑	NH <sub>4</sub> Cl ↓	Adrenal-ectomy ↓	Hypophysectomy ↓	Protein
Stress	+	+	+(?)	+(?)	+
LAP	+	+	+	0(?)	+
DCA	+	+	0	0	0
Endocrine kidney	0	0	0(?)	0(?)	0

#### IV. CLINICAL IMPLICATIONS

Several recent publications indicate that the diseases of adaptation develop in man essentially in the same manner as in experimental animals. It is particularly noteworthy that increased corticoid elimination in the urine has been demonstrated by actual bioassay (Venning and Browne, 1945; Venning and Kazmin, 1946); that the adrenal-cortex of man increases in width and activity (as judged by histologic studies) following exposure to non-specific damage (Zamchek, unpublished); and that renin is present in comparatively high quantities in the blood of the renal vein in man (Haynes et al., 1947). It is true that in hypertensive patients the renin concentration of the kidney vein was not significantly higher than in intact controls, but the procedure (catheterization of the kidney vein) is in itself a damaging agent, and hence the controls can hardly be considered as having been examined under true basal conditions.

It is also significant that in certain types (especially in the malignant types) of nephrosclerosis and hypertension where there is hypochloremia, alkalosis and low sodium diets or treatment with ammonium chloride sometimes prove highly effective in depressing the blood pressure (Viersma, 1946; Selye, 1946), and that diets consisting mainly of rice and fruit juices (Kempner, 1945) likewise tend to depress the blood pressure in hypertensive patients. In the light of the above experimental investigations it is highly

improbable that these rice and fruit juice diets act by virtue of some hypothetic, specific depressor substance contained in them; such food is extremely poor both in sodium and in protein which, in itself, could explain its beneficial action.

### SUMMARY AND CONCLUSIONS

The principal observations upon which the concept of the "General-Adaptation-Syndrome" and the "Diseases of Adaptation" is based have been reviewed with references to the main pertinent literature. Special emphasis has been placed upon certain recent observations indicating that a number of metabolic factors can modify the pathogenicity of mineralo-corticoids produced in response to stress. Thus diets poor in sodium and protein as well as treatment with acidifying salts (e.g.,  $\text{NH}_4\text{Cl}$ ,  $\text{CaCl}_2$ ) tend to prevent the development of nephrosclerosis and hypertension under various experimental conditions.

Clinical observations indicate that in man the diseases of adaptation develop essentially in the same manner as in experimental animals and are accompanied by similar hormonal derangements. In certain cases low-protein diets or treatment with ammonium chloride proved beneficial, but this was not invariably the case, and much further work will be required before the results of the above experimental investigations can be fully utilized in clinical medicine.

### ACKNOWLEDGMENTS

This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service and by the Commonwealth Fund.

### BIBLIOGRAPHY

- ALBRIGHT, F.: Cushing's syndrome. Its pathological physiology, its relationship to the adreno-genital syndrome and its connection with the problem of the reaction of the body to injurious agents ("Alarm Reaction" of Selye), Harvey Lect., 1942-43, xxxviii, 123.
- ALBRIGHT, F.: The relation of the adrenal gland to damage, Cushing's syndrome and the alarm reaction, Conference on Bone and Wound Healing, 3rd Meet., March 12-13, 1943, 12.
- BRAUN-MENENDEZ, E., FASCILOLO, J. C., LELOIR, L. F., MUNOZ, J. M., and TAQUINI, A. C.: "Hipertension arterial nefrogena," 1943, Libreria y Editorial "El Atenco," Publ., Buenos Aires.
- BRAUN-MENENDEZ, E., FASCILOLO, J. C., LELOIR, L. F., MUNOZ, J. M., and TAQUINI, A. C.: "Renal Hypertension." Translated from the Spanish by L. Dexter, 1946, C. C. Thomas, Springfield.
- CANNON, W. B.: The wisdom of the body, 1932, W. W. Norton and Co., Inc., New York.
- CARRIERE, G., and HURIEZ, CL.: Le sang des hypertendus, 1936, G. Doin et Cie.
- CRILE, G. W., and LOWER, W. E.: Anoci-Association, Amy F. Rowland, Ed., 1915, W. B. Saunders Co., Philadelphia.
- DE LA BALZE, F. A.: El síndrome de adaptacion, *Dia Med.*, 1946, xviii, 549.
- DUMONT, L.: Contributions à l'étude de l'hypertension artérielle par ischémie rénale. Université de Liège. Thèse d'agrégation de l'enseignement supérieur, 1946.
- FISHBERG, A. M.: Hypertension and nephritis, 4th Ed., 1939, Lea and Febiger, Philadelphia.

- GALLAVERDIN, L.: La tension artérielle en clinique, sa mesure, sa valeur séméiologique, 2nd Ed., 1920, Masson et Cie.
- GOLDRING, W., and CHASIS, H.: Hypertension and hypertensive disease, 1944, Commonwealth Fund, New York.
- GOLDRING, W., et al.: Experimental hypertension, R. W. Miner, Ed., Special Publications of the New York Academy of Science, 1946, iii, 1.
- HAYNES, F. W., DEXTER, L., and SEIBEL, R. E.: Am. Jr. Physiol., 1947, cl, 198.
- HAYNES, F. W., and DEXTER, L.: Am. Jr. Physiol., 1947, cl, 190.
- HUEPER, W. C.: Arteriosclerosis, Arch. Path., 1944-45, xxxviii, 162, 245, 350; xxxix, 51, 117, 187.
- INGLE, D. J.: Problems relating to the adrenal cortex, Endocrinology, 1942, xxxi, 419.
- KEMPNER, W.: North Carolina Med. Jr., 1945, vi, 117.
- KNOWLTON, A. I., et. al.: Endocrinology, 1946, xxxviii, 315.
- LAFLAQUIERE, J.: Le choc traumatique. I. Le développement du choc expérimental; ses "Périodes," 1942, Société Anonyme de l'imprimerie, A. Roy, Lyon.
- LEBLOND, C. P.: Le syndrome non spécifique (réaction d'alarme de Selye), Ann. d'endocrinol., 1939, i, 179.
- LICHTWITZ, LEOPOLD: "Nephrosis," 1942, Grune and Stratton, New York.
- MAITRE, P.: Le choc traumatique. II. Considérations sur l'origine des "périodes" de l'état de choc et sur l'équilibre glycémique, 1942, Société Anonyme de l'imprimerie, A. Roy, Lyon.
- OVERBEEK, G. A.: Bijnier En Resistentie, Het Hormoon, 1947, xi, 121.
- PAGE, I. H., and CORCORAN, A. C.: Arterial hypertension. Its diagnosis and treatment, 1945, The Year Book Publ., Inc., Chicago.
- SAYERS, G., and SAYERS, M. A.: Endocrinology, 1947, xl, 265.
- SELYE, H., and STONE, H.: Jr. Urol., 1946, lvi, 399.
- SELYE, F. L.: Canad. Med. Assoc. Jr., 1946, lv, 445.
- SELYE, H.: The alarm reaction, Cyclopedia of Medicine, Ed. by E. M. Piersol and E. L. Bortz, 1940, xv, 15, F. A. Davis Co., Philadelphia.
- SELYE, H.: La reaction de alarma, Medicina (Buenos Aires), 1941, ii, 3.
- SELYE, H.: General adaptation syndrome. Conference on Metabolic Aspects of Convalescence including bone and wound healing, 8th Meet., Edward C. Reifenshtein, Ed., Oct. 13-14, 1944, N. Y.
- SELYE, H.: The general adaptation syndrome and the diseases of adaptation, Jr. Clin. Endocrinol., 1946, xi, 117.
- SELYE, H.: Le syndrome général d'adaptation et les maladies de l'adaptation, Ann. d'endocrinol., 1946, xii, 289.
- SELYE, H.: Textbook of endocrinology, Publ. by Acta Endocrinologica, 1947, University of Montreal, Canada.
- SUNDSTROM, E. S., and MICHAELS, G.: The adrenal cortex in adaptation to altitude, climate and cancer, Mem. Univ. Calif., 1942, xii, 1.
- TEPPERMAN, J., ENGEL, F. L., and LONG, C. N. H.: A review of adrenal-cortical hypertrophy, Endocrinology, 1943, xxxii, 373.
- TRUETA, J., et al.: Studies of the renal circulation, 1947, Blackwell Scientific Publications (England).
- VARANGOT, J.: Choc traumatique et hormone cortico-surrénale, Presse méd., 1940, xlviii, 103.
- VENNING, E. H., and BROWNE, J. S. L.: Fed. Proc., 1945, iv, 108.
- VENNING, E. H., and KASMIN, V.: Endocrinology, 1946, xxxix, 131.
- VIERSMA, H. J.: De Behandeling van Hypertensie met Zoutloos Dieet en met uitdrijving van Keukenzout. Een klinische en Haemodynamische Studie, 1946, N. V. Noord-Hollandsche Uitgevers Mattschappij, Amsterdam.

# SERIAL ELECTROCARDIOGRAPHIC CHANGES IN YOUNG ADULTS WITH ACUTE RHEUMATIC FEVER; REPORT OF 62 CASES \*

By NORMAN S. BLACKMAN,† M.D., *Brooklyn, New York*, and CHARLES I.  
HAMILTON, JR.,‡ M.D., *Placerville, California*

## INTRODUCTION

### Purpose and Material

ALTHOUGH no electrocardiographic pattern is specific or diagnostic of acute rheumatic carditis, it is well known that changes do occur which can be correlated with the clinical findings of this disease. Abnormalities of the electrocardiogram which are often seen in acute rheumatic fever have also been recorded in other diseases such as pneumonia, diphtheria, influenza, brucellosis, and typhoid. The value of the electrocardiogram in the diagnosis of myocarditis is well established.<sup>1</sup>

It is generally accepted that increase in the PR interval frequently occurs in acute rheumatic carditis. Less well-known abnormalities of the electrocardiogram have been reported, such as elevation or depression of the R-T or S-T segments,<sup>2, 3, 4</sup> S<sub>-1</sub>, Q<sub>-3</sub> and Q<sub>-1</sub>, S<sub>-3</sub> patterns,<sup>5</sup> prolongation of the duration of electrical systole (Q-T interval),<sup>6</sup> low voltage T-waves,<sup>7</sup> straightening of the ST or RT border,<sup>4, 8</sup> and the occurrence of "the coronary T-wave."<sup>9</sup>

It is the purpose of this article to present the electrocardiographic changes found during the course of the initial attack of proved rheumatic fever in a group of 62 young, white males. This group was made up of soldiers ranging in age from 17 to 21 who entered the Fort George Wright Regional and Station Hospital between January 1, 1946 and April 25, 1947. Each of these cases was under our personal clinical observation.

In no instance was there a previous history of rheumatic fever or chorea per se. Ten members of our group, however, had a history of fleeting joint pains or epistaxis or both at some time during their childhood.

In every instance the chief complaint was subacute or acute arthritis involving one or more joints of the four extremities. On entry these patients had a fever ranging between 99.8° F. and 105° F. orally. A leukocytosis ranging from 11,000 to 20,000 was found in each case on the day of entry. In all but one case there was an elevation of the sedimentation rate above 25 mm. per hour (Westergren method) during the period of hospitalization.

\* Received for publication January 17, 1948.

† Formerly Captain, M. C., Chief of Medicine, AAF Regional Station Hospital, Fort George Wright, Washington.

‡ Formerly Captain, M. C., Chief of Medicine, Station Hospital, Fort Francis E. Warren, Cheyenne, Wyoming.

A mitral systolic murmur of varying intensity was found in 80 per cent of the cases on the first day of entry. Pleuritic chest pain associated with crepitant râles was found in 32 per cent of the cases. A tachycardia was present in 90 per cent of our cases on the day of entry.

In all members of this group, initial treatment consisted of bed rest and 5 to 15 grams of sodium salicylate, orally administered daily in divided doses. Supportive treatment consisted of vitamin supplements in addition to a high caloric diet as tolerated and the cautious administration of parenteral fluids in a few cases evidencing dehydration on entry. Electrocardiograms were obtained every other day during the first week of hospitalization and twice a week thereafter. These patients were followed for a period of six weeks and then were transferred to a General Hospital for convalescence of varying periods. It should be emphasized that in the present study we are concerned only with the initial attack of acute rheumatic carditis and not with the problems of the disease process as presented by chronic rheumatic heart disease.

Our methods of measuring our electrocardiograms and our criteria for abnormality are given as follows: We routinely obtained two Lead III's in each case; Lead IIIa was taken with normal respiration and Lead IIIb was taken during held inspiration. The PR intervals were measured in Lead II routinely and the duration of the QT intervals was taken as the longest QT interval in any of the limb leads. The QT interval was considered prolonged when  $K$  in the formula  $QT = K \sqrt{\text{cycle}}$  exceeded 0.40 second. The precordial lead was taken routinely at CF4, but it was not thought to be constant enough for technical reasons to be taken as an accurate measurement for the purposes of this study. All changes reported in our table of abnormalities occurred in the limb leads. In all instances, unless specifically qualified, our criteria were based upon those given by the New York Heart Association and adopted and distributed by the American Heart Association.<sup>10</sup> Left deviation of the electrical axis was considered present only when the algebraic sum of the QRS deflections was positive in Lead I and negative in Lead IIIb (taken during held inspiration). Similarly, right deviation of the electrical axis was considered present when the algebraic sum of the QRS deflections was negative in Lead I and positive in Lead IIIb. A tendency towards right deviation of the electrical axis was reported when QRS deflections in Lead I equalled zero and were positive in Lead IIIb.

#### CASE PRESENTATIONS

We have selected six cases which we believe to be representative of our group and which gave evidence of electrocardiographic changes that we considered to be abnormal and of particular interest.

*Case 1.* A 21 year old white male entered the hospital with a chief complaint of polyarthrititis and pleuritic-like chest pains of three days' duration. A diagnosis of acute rheumatic fever was made on the basis of acute polyarthrititis, fever, leukocyto-



sis and an elevation of the sedimentation rate to 40 mm. per hour. A tachycardia and a transitory mitral systolic murmur were present on entry. Rheumatic pneumonitis was diagnosed clinically, and a patchy infiltration of the pulmonary parenchyma was seen in the roentgenogram of the chest. Serial electrocardiograms revealed a transitory, first degree auricular ventricular block and the development of an  $S_{-1}$ ,  $Q_{-3}$  pattern (figure 1). An  $S_{-2}$  over 3 mm. was present. The point of particular interest was the development of the  $S_{-1}$ ,  $Q_{-3}$  pattern. Although a deep  $S_{-1}$  was present on the initial record,  $Q_{-3}$  did not become pronounced until three days later. At that time it was more than 25 per cent of the largest QRS deflection in any of the limb leads. This pattern developed with a prolonged, severe, rheumatic pneumonitis, a rheumatic carditis, and a mitral systolic murmur.

*Case 2.* A 17 year old white male entered the hospital with the chief complaint of polyarthritis, pleuritic-like chest pains and marked dyspnea of 24 hours' duration. On entry the patient had rheumatic pneumonitis confirmed by roentgenogram, a gallop rhythm, and a pericardial friction rub. The pericardial rub persisted for 24 hours. A grade II mitral systolic murmur and extension of the area of cardiac dullness 2 cm. to the left of the midclavicular line were found on physical examination. His sedimentation rate was 90 mm. per hour. Associated with the pericarditis, the patient's electrocardiogram revealed the following (figure 2): Elevation of the  $ST_{-1}$  and  $ST_{-2}$  segments; a prolonged PR interval;  $T_{-1}$  less than 1 mm.,  $T_{-2}$  diphasic and  $T_{-3}$  inverted. Of particular interest was the "coronary type T-wave" seen in  $CF_4$ , on September 19, 1946 (the "coronary T-wave form" consists of an upward convexity of the ST or RT segment with an inverted T-wave). On September 24, 1946, a "coronary type T-wave" was seen in Lead I as well as Lead IV;  $T_{-1}$  was then inverted to diphasic and  $T_{-4}$  was sharply inverted;  $T_{-2}$  was diphasic and  $T_{-3}$  was upright to diphasic, but low. In this tracing, too, it should be noticed that the previously elevated ST segments in Leads I and II returned to the iso-electric line, having borne a time relation to the clinical evidence of pericarditis. On the tracing of October 3, 1946, the "coronary T-wave form" entirely disappeared;  $T_{-1}$  was flat;  $T_{-2}$  was upright, but low;  $T_{-3}$  was flat and  $T_{-4}$  was upright. A low  $R_{-4}$  was seen in the Lead  $CF_4$  on this date. This may have been due to failure in placing the precordial lead in the same position used previously and subsequently. The record of October 31, 1946 showed a return of the pattern toward normal.  $T_{-1}$  and  $T_{-2}$  were upright and normal, and  $T_{-3}$  was upright to flat. Straightening of the ST border was present in this record in Leads I and II. The electrocardiogram on November 4, 1946 was essentially normal although some straightening of the  $ST_{-1}$  border was still present. This case represents a severe clinical pericarditis and myocarditis.

*Case 3.* A 19 year old male entered the hospital with the chief complaint of polyarthritis. On the day of entry he had a leukocytosis, fever and rheumatic pneumonitis. We are mentioning this case because it showed a change from a tendency to right deviation of the electrical axis to unequivocal right axis deviation and because it showed the formation of an  $S_{-1}$ ,  $Q_{-3}$  pattern (figure 3). It should be noted at this point that the  $Q_{-3}$  was less than 25 per cent of the height of the QRS segment in any one of the limb leads. We interpret a tendency to right deviation of the electrical axis when the algebraic sum of the QRS deflections in Lead I is zero and Lead III is positive. It will be noticed that this tendency became actual right deviation of the electrical axis in a period of about three weeks.

*Case 4.* A 17 year old white male entered the hospital with the chief complaint of polyarthritis, chills and fever of 24 hours' duration. On the day of entry the patient had a leukocytosis, fever, and a sedimentation rate which was 119 mm. per hour. A tachycardia was present on entry, but there were no murmurs on auscultation of the heart. Within the 48 hours after entry the patient developed a grade I mitral systolic murmur which persisted until he was transferred to a General Hospital for convalescence. This patient is presented because his electrocardiogram demonstrated

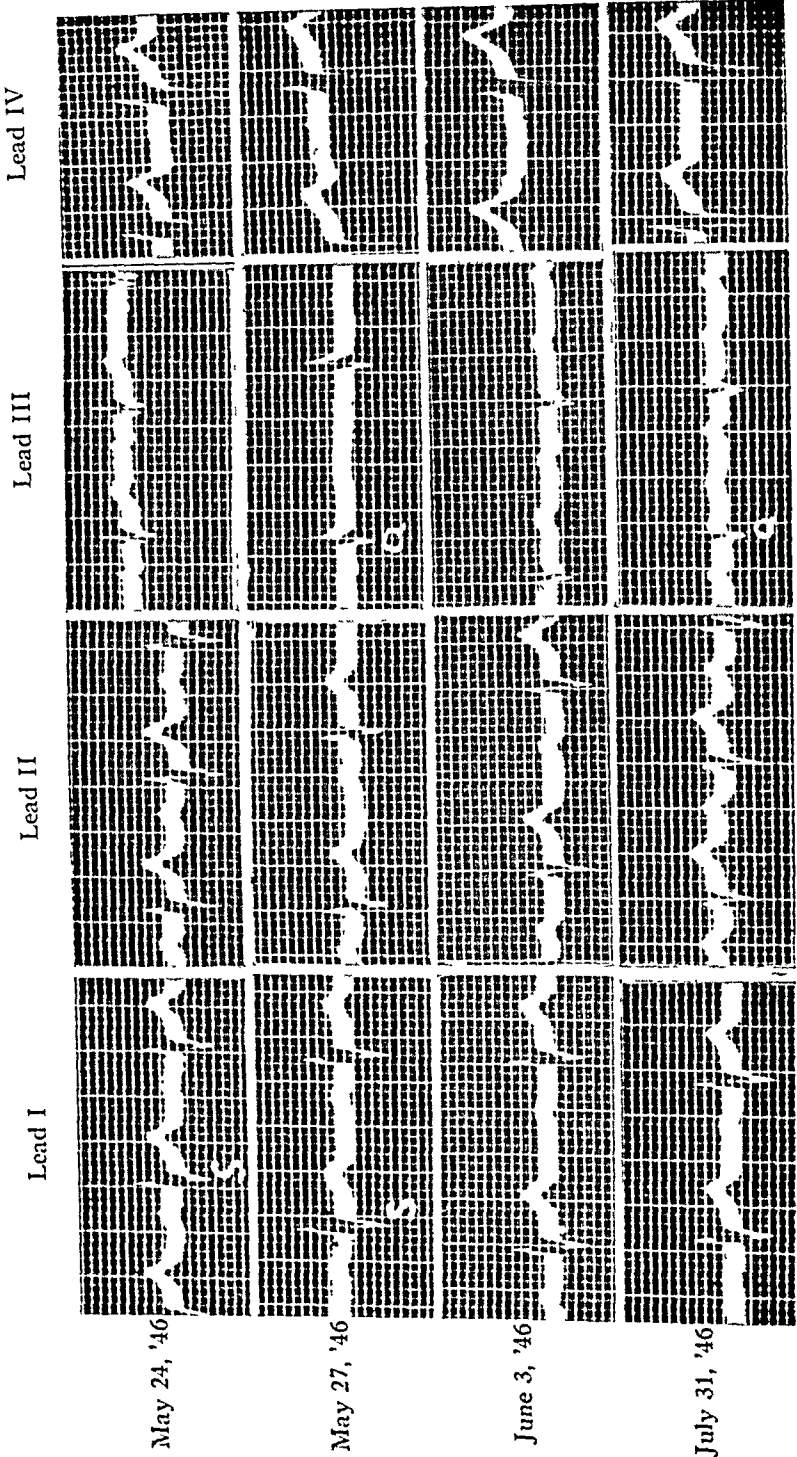


Fig. 1. Case 1. Note development and changing relationships of  $S_{-1}$  and  $Q_{-3}$ .

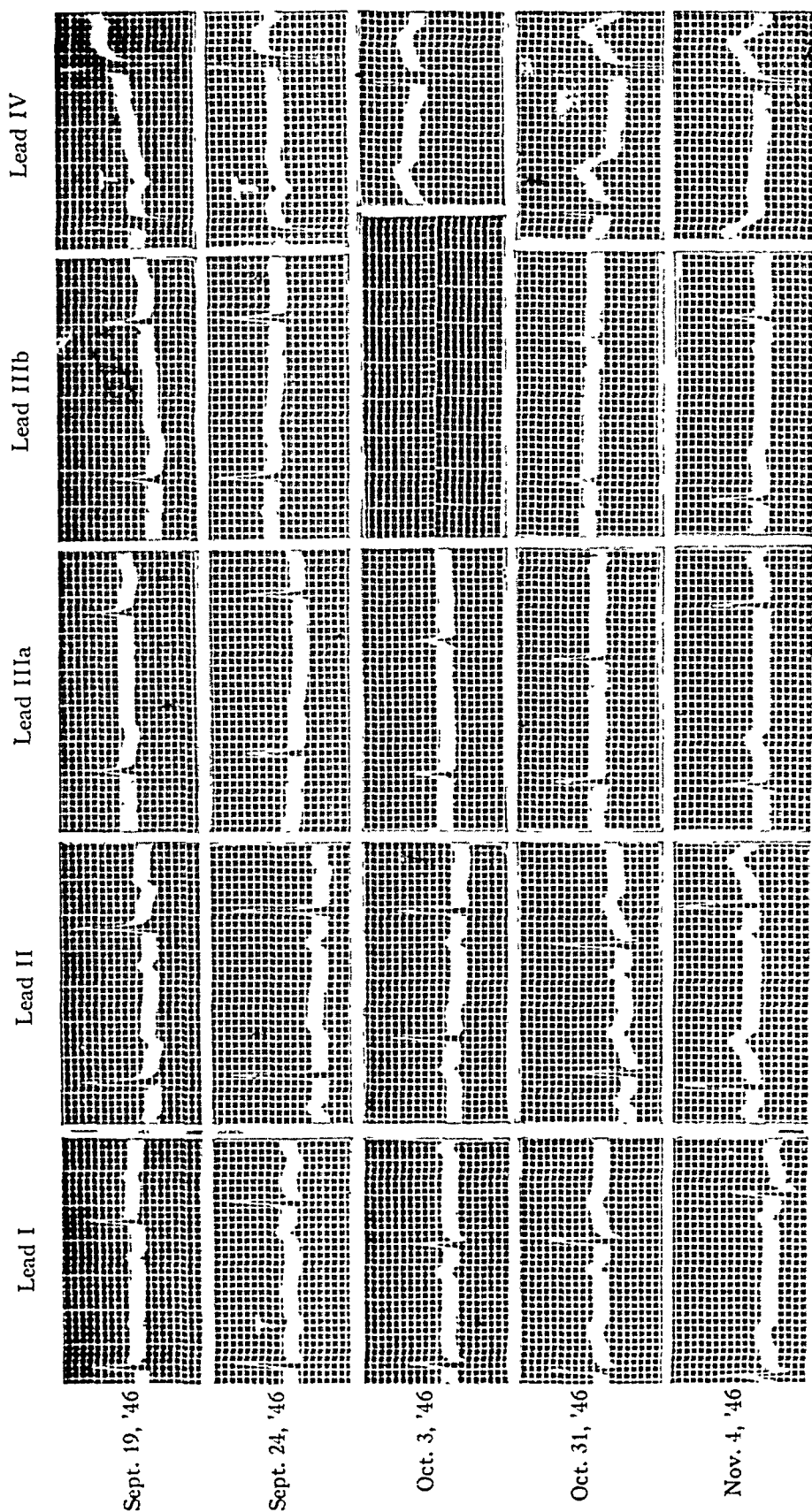


FIG. 2. Case 2. Note development of "coronary T-wave" first in Lead IV of September 19, 1946 and then in Lead I and Lead IV of September 24, 1946.

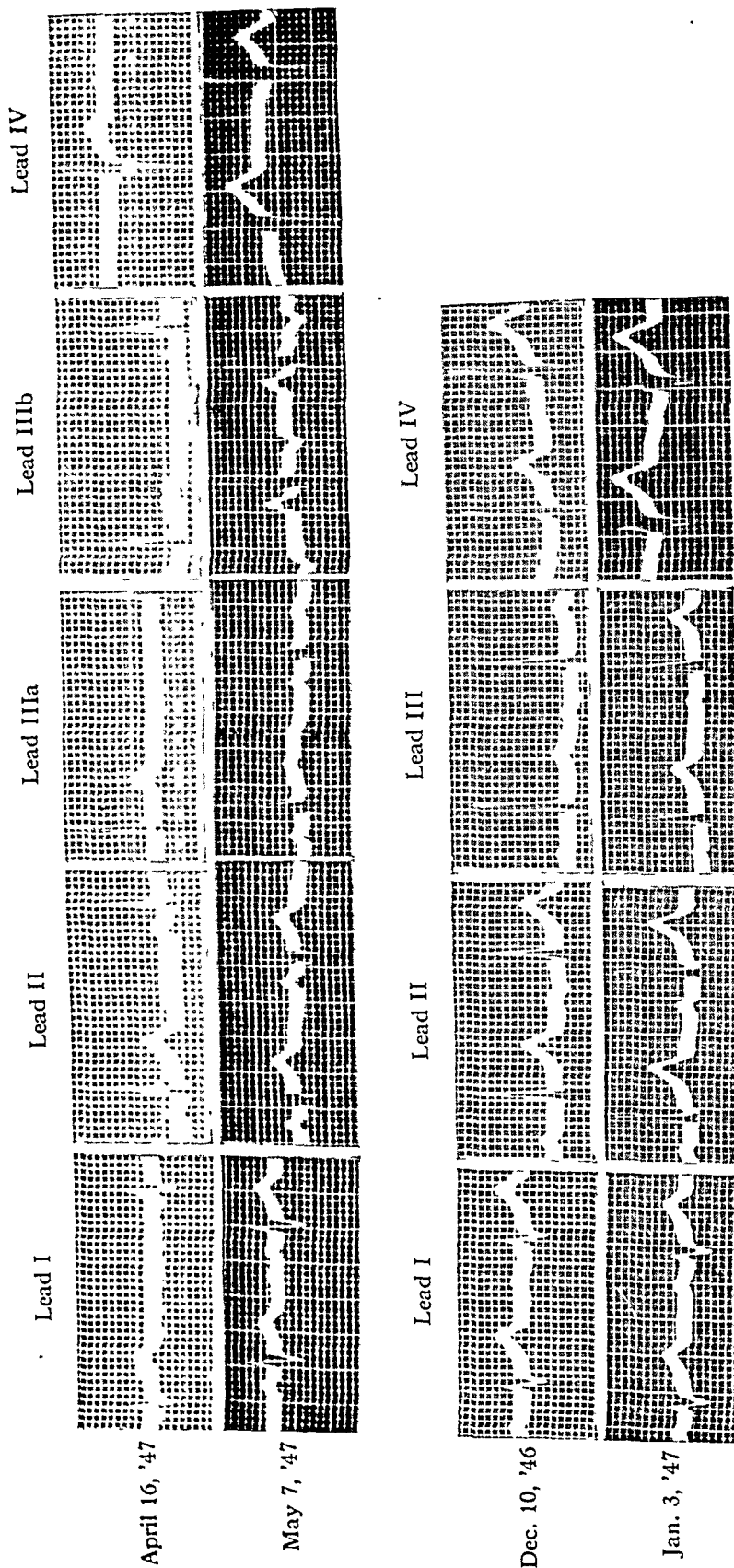


FIG. 3. (above) Case 3. Note shift from tendency to right deviation of the electrical axis to right deviation of the axis between April 16, 1947 and May 7, 1947. (below) Clinical course similar to Case 3 above, but not included in statistics of present report. Note shift toward right axis deviation.

a progressive auricular ventricular block (Wenckebach phenomenon). A slight elevation of the ST segments in Leads I and II was noted during the patient's course in the hospital (figure 4).

*Case 5.* A 17 year old white male entered the hospital with the chief complaint of migratory joint pains of 24 hours' duration. On entry he had acute polyarthritis, pleuritic-like chest pains, fever, sinus tachycardia and a sedimentation rate of 78 mm. per hour. This case is presented because it demonstrated a wandering pace-maker. Forty-eight hours after demonstrating the latter, the electrocardiogram was found to have a PR interval of .28 second. The first degree heart block is not illustrated.

*Case 6.* A 20 year old soldier entered the hospital with the chief complaint of polyarthritis and palpitation of one week's duration. A diagnosis of acute rheumatic fever was made on the basis of an elevated sedimentation rate which was 50 mm. per hour on entry, leukocytosis, tachycardia, polyarthritis, fever, and a grade I mitral systolic murmur with a changing electrocardiogram. The patient's electrocardiogram has been reproduced to show the prolongation of the duration of electrical systole (QT interval) which was evidenced in Leads I, II, and III, in which K in the formula  $QT = K \sqrt{\text{cycle}}$  was 0.42 second in the longest QT of the limb leads. Of incidental interest is the deep  $S_2$  which projected downward for a distance of 4 mm. (figure 6).

## DISCUSSION

*General.* The electrocardiographic changes in the acute phase of rheumatic carditis are based on the changing inflammatory state of the tissue reaction of the heart. The pathology of this state is well known to consist of acute inflammation, edema and leukocytic infiltration of the heart tissues. Aschoff's bodies in the interstitial tissue and a rheumatic arteritis are invariably present. It is not strange, therefore, that, with such alterations in the pericardium, myocardium, valves and blood vessels, a corresponding alteration in the physiology and anatomy of the heart takes place.

It was often found in the course of our investigation that a single electrocardiogram was interpreted as normal, but that subsequent records, themselves probably within normal limits, showed peculiar variations from record to record on the same patient. The concept of a changing inflammatory state of the myocardium giving rise to a changing pattern on serial records is vital to the understanding of the electrocardiograms of acute rheumatic carditis. Although any particular record in a patient's series might be interpreted as within normal limits, inspection of the serial records of the patient left no doubt of the abnormality of the series.

In the course of this study, many transient changes were noted in the electrocardiographic patterns. It has been clearly shown that salicylates have no effect whatsoever on the normal electrocardiogram.<sup>11</sup> Extensive studies have shown that salicylates have not been proved to affect in any way even the AV conduction time in acute rheumatic carditis.<sup>12</sup> Therefore, we have concluded that the changes we observed were not due in any part to the salicylate therapy that was given routinely.

Our patients were all bed patients at least for the first three weeks, and the tracings were taken in a recumbent position with a single pillow under the head.

Feb. 28, '47

Feb. 26, '47

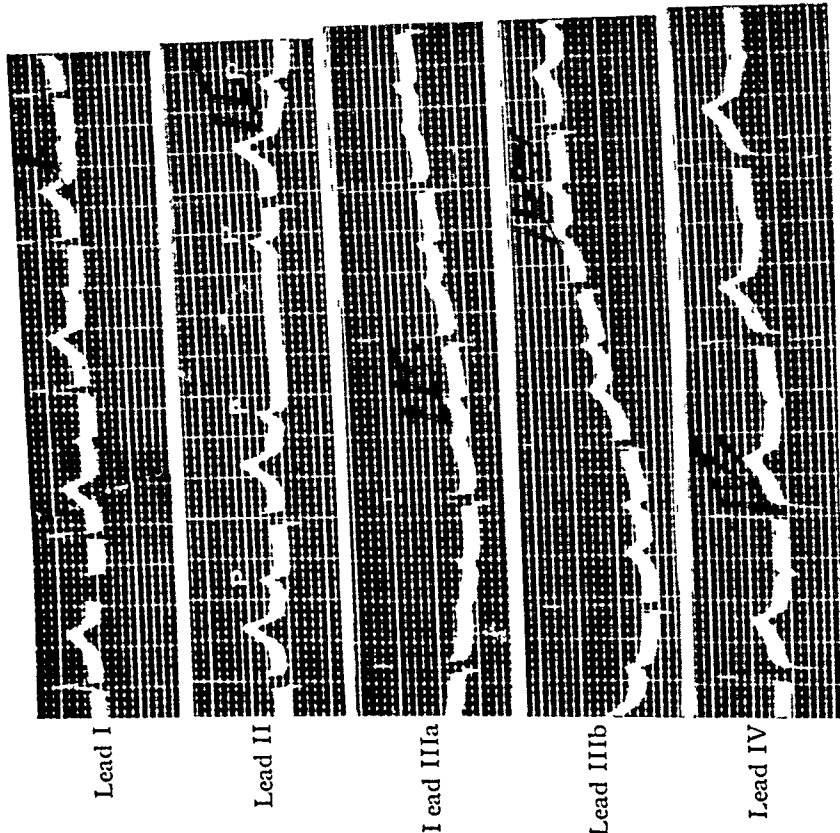
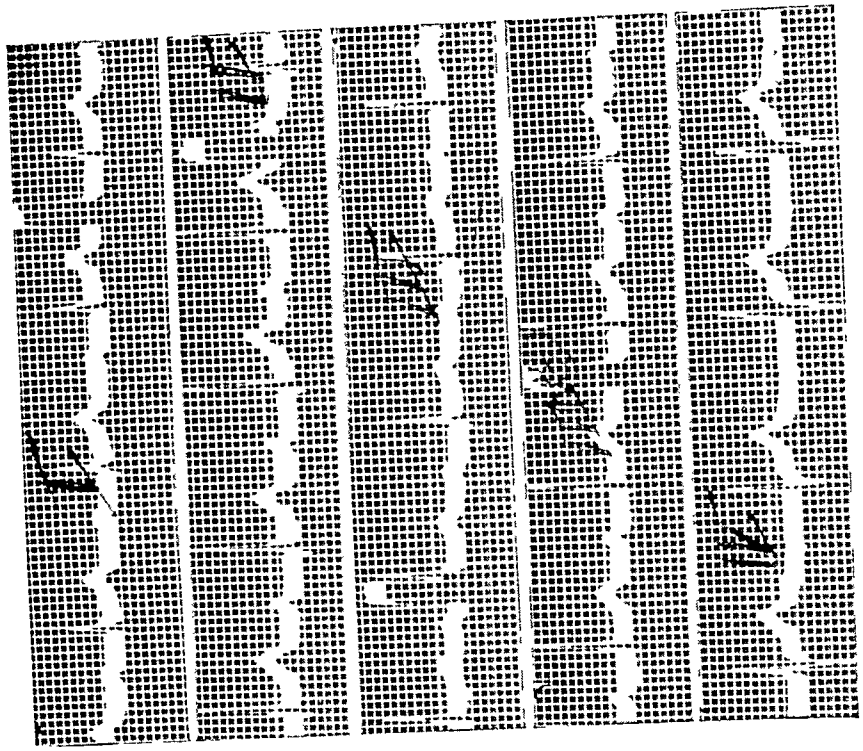


FIG. 4. Case 4. Note increasingly prolonged PR interval with eventual dropping of a beat in Lead II of February 26, 1947.

Feb. 13, '47

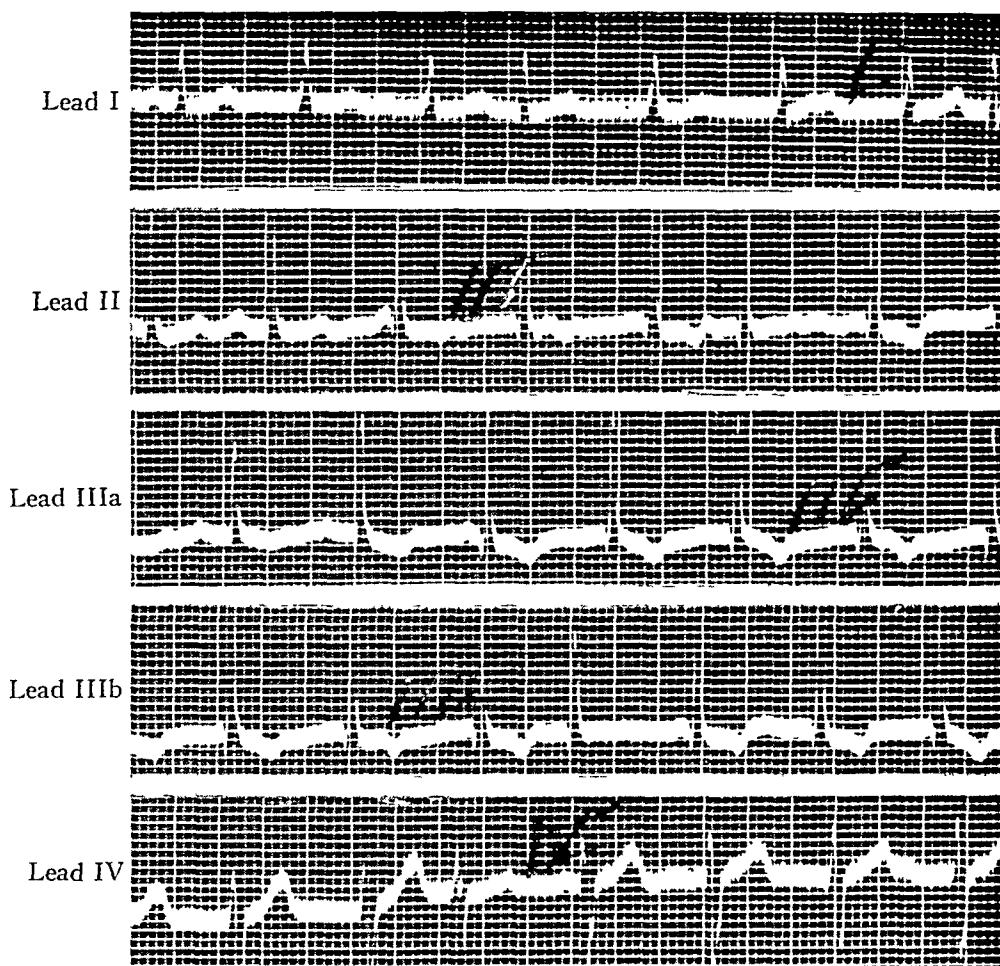


FIG. 5. Case 5, demonstrating a wandering pacemaker.

TABLE I  
Summary of Electrocardiographic Changes Found

Category	Number of Cases	Per Cent of Total
T-wave alteration including changes in the ST segments	38	61.2
First degree, auricular ventricular block	26	41.9
Prolongation of QT interval	22	35.0
Abnormal fluctuation of the level of the ST segments (elevation and depression)	14	22.5
$S_{-1}$ , $Q_{-3}$ pattern	7	11.2
Inversion of limb lead T-waves	7	11.2
$S_{-2}$ greater than 3 mm. without axis deviation	7	11.2
$Q_{-1}$ , $S_{-3}$ pattern	3	4.8
Transitory AV nodal rhythm	3	4.8
Left axis deviation	2	3.2
Right axis deviation	1	1.6
Right bundle branch block	1	1.6
Wenckebach phenomenon	1	1.6
Normal	1	1.6

61 (98.4 per cent) of the 62 patients had one or more of the electrocardiographic changes listed.

We have utilized the fact that the electrocardiographic pattern in a given normal individual remains uniformly constant from time to time and day to day.<sup>8, 13, 17</sup> Alterations in the pattern do, in fact, occur, but these cannot be recognized in the least as distinct and different from one record to another.

*P-R Interval.* As was anticipated, a large number of our cases showed transitory prolonged PR intervals (41.9 per cent) (table 1). All of these

March 21, '47

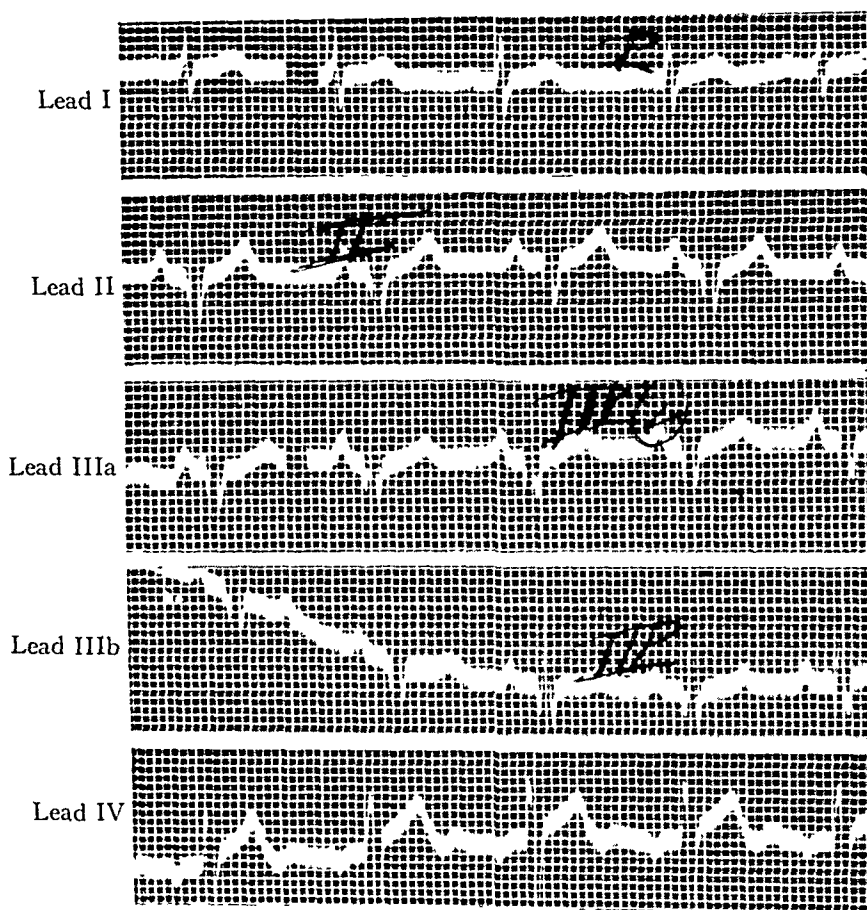


FIG. 6. Case 6. Note prolongation of the duration of electrical systole (Q-T interval).

returned to normal before transfer for convalescence. The return of the PR interval to normal has been looked upon with confidence as a sign of cessation of rheumatic activity. However, in three of our cases with apparent clinical remission and the return of the PR interval from abnormal to normal, a subsequent flare-up occurred with the reappearance of the first degree heart block. Subsequently, the PR intervals returned to normal. These findings seem to indicate that our criteria for quiescence of this disease are far from absolute. Convalescence in this disease should probably be longer than has been generally regarded as sufficient.

A transitory Wenckebach phenomenon showing progressive lengthening



of the PR interval with eventual dropping of the beat was seen in one case (see case 4, figure 4).

No cases of complete AV block were recorded.

*Q-T Interval.* The duration of electrical systole (the Q-T interval) was found to be prolonged in 35 per cent of our cases. A previous study<sup>9, 16</sup> reported that 100 per cent of their cases of acute rheumatic carditis showed prolonged Q-T interval. These cases were primarily children and in a much younger age group than our cases.

The duration of the Q-T interval was determined by calculating K in the formula  $QT \text{ interval} = K \sqrt{\text{cycle}}$ . We considered K to be abnormal when it was greater than 0.40 second in any of the limb leads.

Some observers believe that there is little practical value in measuring the duration of electrical systole (Q-T interval).<sup>14</sup> However, we found its determination to be of some value. In four of our cases of clinical rheumatic fever with rheumatic carditis, it was the only demonstrable deviation in the electrocardiogram.

*Normals.* With serial electrocardiograms taken routinely, as described previously (every other day for the first week and then twice a week thereafter), one (1.6 per cent) of our cases showed entirely normal records throughout the entire period of observation. It is conceivable that if the records had been taken more frequently, transitory abnormalities might have been detected even in this case.

The extent of rheumatic inflammation and its location is probably of some importance as to whether or not changes are recorded in the electrocardiographic tracing. The fact that 98.4 per cent of our patients showed abnormalities in their electrocardiographic series indicates the widespread acute damage that occurred. We assume that the one normal case may have had rheumatic lesions on such a small scale as to be undetectable by the electrocardiogram utilizing the standard leads. Again we emphasize the importance of change in the records. In effect the whole series of electrocardiograms of a given patient is more sensitive in detecting pathologic lesions than any one of the records in the series.

*Rhythms.* A variety of unusual rhythm such as auricular premature contractions, ventricular premature contractions, nodal rhythms, sinus bradycardia and paroxysmal tachycardia were noted but were not included in the present study as abnormal, for these may occur in normal people. However, in the presence of an irritable, inflamed myocardium, they may be of significance. Two cases of wandering pacemaker were recorded. Auricular fibrillation and auricular flutter were not seen. Ventricular rhythms other than ventricular premature contractions did not occur.

*QRS Changes.* There were no records of abnormal forms of the component waves of the QRS complex considered by themselves. However, several deviations which have been thought to be due to strain on the right or left heart became apparent. Cross patterns of S<sub>1</sub>-, Q<sub>-3</sub> and Q<sub>-1</sub>, S<sub>-3</sub> type

were considered present whenever such patterns were found or developed in the course of the disease. We made no attempt to set down criteria for the height of these waves before they should be considered significant. Their mere existence in these combinations has been found to be three times more frequent in children with rheumatic heart disease than in normal children.<sup>5</sup> Although we consider such combinations in themselves suggestive of abnormality, in every case reported with these patterns other evidence of active carditis in the serial electrocardiograms was present.

It may be that such cross patterns represent the early initial phases of the anatomical alteration in the heart which ultimately lead to deviation of the electrical axis, so often seen in rheumatic heart disease. The  $S_{-1}$ ,  $Q_{-3}$  pattern has been thought to represent early right heart strain and the  $Q_{-1}$ ,  $S_{-3}$  pattern early left heart strain. In this connection, Case A with severe rheumatic pneumonitis developed a prominent  $Q_{-3}$  in a period of three days to show a definite  $S_{-1}$ ,  $Q_{-3}$  cross pattern. We postulate that this was due to right heart strain from the burden of an inflamed myocardium, mitral valvular disease, pulmonary disease, and increased pulmonary arterial tension secondary to widespread rheumatic arteritis of the pulmonary vessels.

An  $S_{-1}$ ,  $Q_{-3}$  pattern occurred in 11.2 per cent, and a  $Q_{-1}$ ,  $S_{-3}$  pattern in 4.8 per cent of our cases.

A large number of our cases had rheumatic pneumonitis (32 per cent). Our clinical criteria for such a diagnosis were the rheumatic picture plus dyspnea, pleuritic pain on respiration, crepitant râles and roentgen-ray evidence of patchy infiltration in the vast majority of the cases so diagnosed.

When no deviation of the electrical axis was present, 11.2 per cent of our cases showed an  $S_{-2}$  which was less than 3 mm. initially and which became greater than 3 mm. during the period of hospitalization. The significance of this finding is not clear, but it did occur in a sizeable percentage of our cases of acute rheumatic carditis. An  $S_{-2}$  greater than 3 mm. in the absence of axis deviation may occur normally, but it may also be associated with evidence of organic heart disease.<sup>15</sup>

Surprisingly few cases showed axis deviation. Left deviation of the electrical axis was seen in 3.2 per cent of our group. Frank deviation of the electrical axis to the right was seen in only one case. In general then, it appears that deviation of the electrical axis is primarily a manifestation of prolonged established rheumatic heart disease.

*RT or ST Period and T-Wave Changes.* "The period from the end of the R-wave or S-wave to the end of the T-wave may be divided into two portions; the first portion terminates at the onset of the T-wave and the second portion is occupied by the T-wave itself. Alterations may be distinguished which involve these segments either separately or together."<sup>8</sup> In the normal electrocardiogram at the conclusion of the R-wave or S-wave, a short iso-electric period (RT or ST segment) occurs during which a slight upward slope may be present. This is followed by a definite change in the direction of the slope of the string to begin the T-wave.

Alterations in the second portion, or T-wave, consist of high voltage T, low voltage T, flat T, inverted T, peaking of T, and asymmetry of T. We took two Lead III's in order to lessen the normal variation that is usually seen in the T-wave of this lead. Lead IIIa was taken as the usual records with normal respiration. Lead IIIb, however, was taken in held inspiration.

Changes in the first portion (RT or ST segment) of the curve were mostly confined to fluctuations in the elevation and depression of these segments as compared to the level of the PR interval as a baseline (figure 7). These changes occurred in 22.5 per cent of our cases. In cases of clinical pericarditis and anoxemia of the heart muscle, changes in the level of the RT

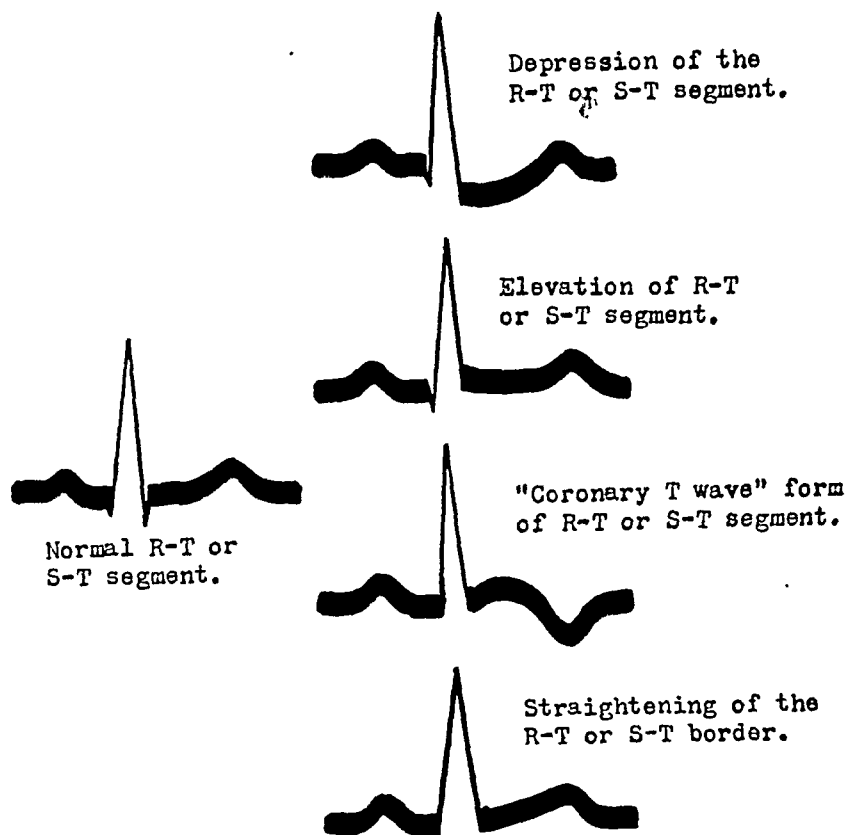


FIG. 7. Abnormalities of the R-T or S-T segment.

or ST segments have been observed. It has been shown repeatedly that unchanging slight elevation or depression of these segments per se are of no great clinical importance. Fixed elevation of this segment is frequently seen in the chronic phase of rheumatic heart disease. This is not found characteristically in acute rheumatic activity and is probably due to myocardial fibrosis secondary to the residual pathologic lesions associated with acute attacks of rheumatic inflammation. Indeed, fixed elevation of this segment has often been seen in perfectly normal individuals.<sup>15, 17</sup> We did not consider any of our cases to have abnormalities of the RT or ST seg-

ment which did not show a continual changing, fluctuating position of the segment, varying between elevation and depression, of 1 mm. or more.

The changes seen as a combination of the RT or ST segments and the T-wave consisted of the occurrence of the "coronary T-wave," and the straightening of the ST or RT border. Both of these abnormalities are shown on the record of case 2 and figure 2 (see also figure 7).

The "coronary T-wave" consists of a downward directed T-wave with an RT or ST interval showing an upward convexity which lies at the zero point of the record or above it.<sup>9</sup> Although this change is often seen in coronary disease, it has also been implicated in rheumatic carditis and may be due to pericarditis with complicating myocarditis.<sup>3,9</sup>

Straightening of the RT or ST border consists merely of the loss of the change of slope of the line which normally begins at the beginning of the T-wave. This results in a straight sloping line from the end of R or S to the peak of T (figure 7). This occurred in 28 (45 per cent) of our cases and was most frequently found in Leads I and II. High voltage T-waves (greater than 0.5 mv.) were found in 20 cases and were always associated with straightening of the ST border. It will be seen from table 1 that the most frequent changes observed occurred in the T-wave portion of the tracing (61.2 per cent). We found then that the RT or ST period and the T-wave portion of the curve changes more frequently away from the normal in this disease than does the duration of the PR interval (41.9 per cent in our series) which has been thought to be one of the most frequent changes in the electrocardiogram of rheumatic carditis.

### GENERAL DISCUSSION

It should be noted that in all cases presented the changes are transient and indicate the transitory damaging effect of the acute rheumatic involvement of the heart. This is easily understandable in the light of the well-known transitory manifestations of this disease in the joints, skin, lungs, and other tissues. That permanent damage does occur is beyond dispute, but apparently the amount of tissue attacked in the initial phases is far more extensive than that in which chronic damage remains.

All of the 98.4 per cent of cases showing abnormalities in their serial records showed these changes within the first two weeks of the onset of the clinical symptoms. Therefore, by taking between five and six records during these first two weeks, valuable objective confirmatory evidence of rheumatic carditis was recorded. The routine suggested is an electrocardiogram taken every other day for the first week, and an electrocardiogram twice in the second week. We believe this routine to be both practical and economical in the use of the electrocardiogram as contributory evidence in the diagnosis of suspected clinical rheumatic fever. A high expectation of confirmatory evidence by demonstration of abnormalities described in this paper can be expected.

## SUMMARY AND CONCLUSIONS

The electrocardiographic findings of serial electrocardiograms in 62 cases of the initial attack of proved acute rheumatic fever in young adults are presented. These findings are correlated with the clinical course in six particularly interesting cases.

If records are taken every other day during the first week and twice a week thereafter in cases of acute rheumatic fever, a high percentage of abnormal serial electrocardiograms due to rheumatic carditis will be obtained. This is of considerable value in the differential diagnosis of this disease.

A much larger number of cases showed changes in the RT or ST segment and T-waves (61.2 per cent) than showed prolonged PR intervals (41.9 per cent). This seems to indicate that rheumatic activity, as demonstrated by electrocardiographic changes, more often affects the ventricular myocardium than the A-V conduction tissue alone.

The return of the electrocardiogram to normal cannot be taken as a criterion for complete remission of rheumatic activity.

Although minor variations of the electrocardiographic pattern probably do occur in normal individuals, these are extremely slight and not recognizable as abnormal fluctuations. The most valuable single concept of the electrocardiogram in the diagnosis of rheumatic carditis is that of the changing pattern in serial records corresponding to the changing inflammatory state of the heart, to show abnormal fluctuations during the course of the disease.

## BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, 2nd Ed., 1942, Macmillan Co., New York.
2. PARDEE, H. E. B.: Electrocardiographic findings in rheumatic heart disease, *Am. Jr. Med.*, 1947, ii, 528.
3. PARDEE, H. E. B.: Clinical aspects of the electrocardiogram, 4th Ed., 1942, Paul B. Hoeber, Inc., New York.
4. ROTHSCHILD, M. A., SACKS, B., and LIBMAN, E.: The disturbances of the cardiac mechanism in subacute bacterial endocarditis and rheumatic fever, *Am. Heart Jr.*, 1927, ii, 356.
5. CROSSFIELD, H. C.: Electrocardiograms in rheumatic heart disease in children, *Am. Jr. Med.*, 1946, i, 36.
6. TARAN, L. M., and SZILAGI, N.: The duration of electrical systole (Q-T) in acute rheumatic carditis in children, *Am. Heart Jr.*, 1947, xxxiii, 14.
7. MASTER, A. M.: Low voltage T-waves in the electrocardiogram, *Am. Jr. Med. Sci.*, 1931, clxxxi, 211.
8. COHN, A. E., and SWIFT: Electrocardiographic evidence of myocardial involvement in rheumatic fever, *Jr. Exper. Med.*, 1924, xxix, 1.
9. PORTE, D., and PARDEE, H. E. B.: The occurrence of the coronary T-wave in rheumatic pericarditis, *Am. Heart Jr.*, 1929, iv, 584.
10. Criteria committee of the New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart, 4th Ed., 1945, New York Heart Assoc., New York.
11. MASTER, A. M.: The effect of sodium salicylate on the normal human electrocardiogram, *Am. Heart Jr.*, 1927, iii, 180.

12. WYCKOFF, J., DEGRAFF, A. C., and PARENT, S.: The relationship of the auriculo-ventricular conduction time in rheumatic fever to salicylate therapy, *Am. Heart Jr.*, 1930, v, 586.
13. COHN, A. E.: An investigation of the relation of the position of the heart to the electrocardiogram, *Heart*, 1921-22, ix, 311.
14. KATZ, L. M.: *Electrocardiography*, 1941, Lea and Febiger, Philadelphia, p. 97.
15. GRAYBIEL, A., and WHITE, P. D.: *Electrocardiography in practice*, 1946, W. B. Saunders Co., Philadelphia.
16. TARAN, L. M.: Clinical and laboratory diagnostic criteria of rheumatic fever in children, *Am. Jr. Med.*, 1947, ii, 368.
17. BLACKMAN, N. S.: The normal serial electrocardiogram. To be published.

# NEURONITIS AND NEURONOPATHY: FURTHER EXPERIENCES WITH TYPHOID VACCINE THERAPY \*

By ABRAHAM M. RABINER, M.D., F.A.C.P., MEYER ROSENBERG, M.D., and  
HOWARD FREEDMAN, M.D., *Brooklyn, New York*

ACUTE inflammatory disease of the peripheral nerves and nerve roots, alone or in combination with involvement of the brain, brain stem or spinal cord, has been the subject of numerous reports since the original article by Osler<sup>1</sup> in 1892. These isolated, sporadic cases and groups of cases of almost epidemic proportions have been characterized by protean symptoms and findings. Despite numerous efforts at isolation of a definite causative organism, none has been consistently found, and we have had to accept the general impression that a virus is the most likely etiological factor. Mills,<sup>2</sup> in 1898, first suggested the term "neuronitis" for this disease. In 1916, Guillain, Barré and Strohl<sup>3</sup> reported a series of cases, all of whom recovered. They first drew prominent attention to an increase in spinal fluid protein without any increase in cells and suggested the designation "albumino-cytologic dissociation." They indicated that this implied a good prognosis. In subsequent studies, depending upon the symptomatology of the cases reported, the disease has been reported under many descriptive names such as "infectious polyneuritis," "encephalo-myelo-radiculoneuritis," "infective neuronitis," or simply as the "Guillain-Barré syndrome," even in the absence of albumino-cytologic dissociation.

Since the study of Guillain, Barré and Strohl, numerous reports have challenged the concept that an albumino-cytologic dissociation indicated a good prognosis. In 1918, Bradford, Bashford, and Wilson<sup>4</sup> reported a 26.6 per cent mortality in 30 cases. Gilpin, Moersch and Kernohan,<sup>5</sup> in 1936, reported a 14 per cent mortality in 35 cases, and Forster, Brown and Merritt,<sup>6</sup> in 1941, reported a 42 per cent mortality in 26 cases. DeJong,<sup>7</sup> in 1940, presented 15 cases with a 13.3 per cent mortality. He divided his cases into three types, according to end results: (a) those who recovered completely in an average of eight weeks, (b) those with an incomplete recovery and a prolonged course, (c) those with a fatal termination. He concluded that from the type of onset, early clinical course and laboratory findings, one is unable to foretell the outcome. Roseman and Aring<sup>8</sup> reported 16 cases with an 18 per cent mortality. They estimated the duration of an acute phase from two weeks to four months, and a total duration of illness varying from eight weeks to three years. It seems evident, therefore, that even albumino-cytologic dissociation is not reliable in prognosis as to

\* Received for publication July 25, 1947.

From the Neurologic Service, Kings County Hospital, Brooklyn, New York.

life itself. The duration of illness is often prolonged to three years with residual symptoms still present.

In spite of such uncertainty as to prognosis, treatment has been largely supportive in nature, with emphasis upon physiotherapy, orthopedic appliances, adequate nutrition, relief of pain with analgesics, and more recently the use of thiamine chloride and the nicotinic acid derivatives. None of these measures has been adequate to control almost constant features of the disease: severe pain, muscle tenderness and hyperalgesia. The use of typhoid vaccine to induce fever in cases of this type was suggested in 1930 by Strauss and Rabiner<sup>9</sup> who administered it with good results in four cases, but they drew no definite conclusions because three other cases of a similar type recovered without the vaccine therapy. Mackay<sup>10</sup> mentions its use in one case without effect. Bennett<sup>11</sup> employed it in two cases of brachial plexus neuritis following administration of tetanus antitoxin and reported prompt and complete relief from pain. Individual cases were treated in a similar manner by Schneider<sup>12</sup> and Keschner<sup>13</sup> with good results.

#### CASE REPORTS

*Case 1.* M. F., a waitress, aged 19, entered the Dermatologic Service, Kings County Hospital, February 26, 1946, for treatment of pediculosis and multiple cutaneous abscesses. Local therapy resulted in improvement. On April 11, 1946, she began to complain of numbness and weakness of the left extremities. Neurological examination two days later revealed mild weakness in all extremities with diminished to absent tendon reflexes, impaired sensation to pin and touch over the hands and forearm, especially on the ulnar aspect. An initial spinal fluid examination was negative except for total protein of 125 mg. per cent. All laboratory data were otherwise negative.

Upon transfer to the Neurologic Service, the patient was placed on intense vitamin therapy, but her progress was remorselessly downward for the next four weeks. She became almost completely quadriplegic with loss of sensation of a glove and stocking distribution. Facial asymmetry developed with flattening of the right nasolabial fold. Nasal speech and difficulty in swallowing ensued, and urinary retention with overflow incontinence occurred attributed to an atonic bladder as revealed by a cystometrogram. Calf muscle tenderness was severe. Spinal fluid protein remained at the same level.

Intravenous typhoid vaccine therapy was instituted on May 14. Two injections were given over a three day period, beginning with 10 million organisms and terminating with 30 million. Severe exacerbations of pain in the extremities occurred during the periods of temperature elevation. One day after this therapy was begun, for the first time in a month, there was a definite decrease in the deep muscle tenderness, with complete disappearance of this complaint in 14 days. Urinary incontinence ceased the day following the first typhoid injection. Motor power began to improve three days after therapy was instituted and continued, so that by June 14, one month later, the patient was out of bed and able to perform routine functions, and in another three weeks could walk unsupported. Sensation improved in less dramatic fashion but was almost normal within five weeks. The patient was discharged on August 2, at which time the only abnormalities were absent tendon reflexes, minimal hypalgesia of a glove and stocking type, and an atonic bladder.

*Comment.* This case presented a severe peripheral neuropathy with hyperalgesia so marked as to suggest radicular involvement. An albumino-cytologic dissociation



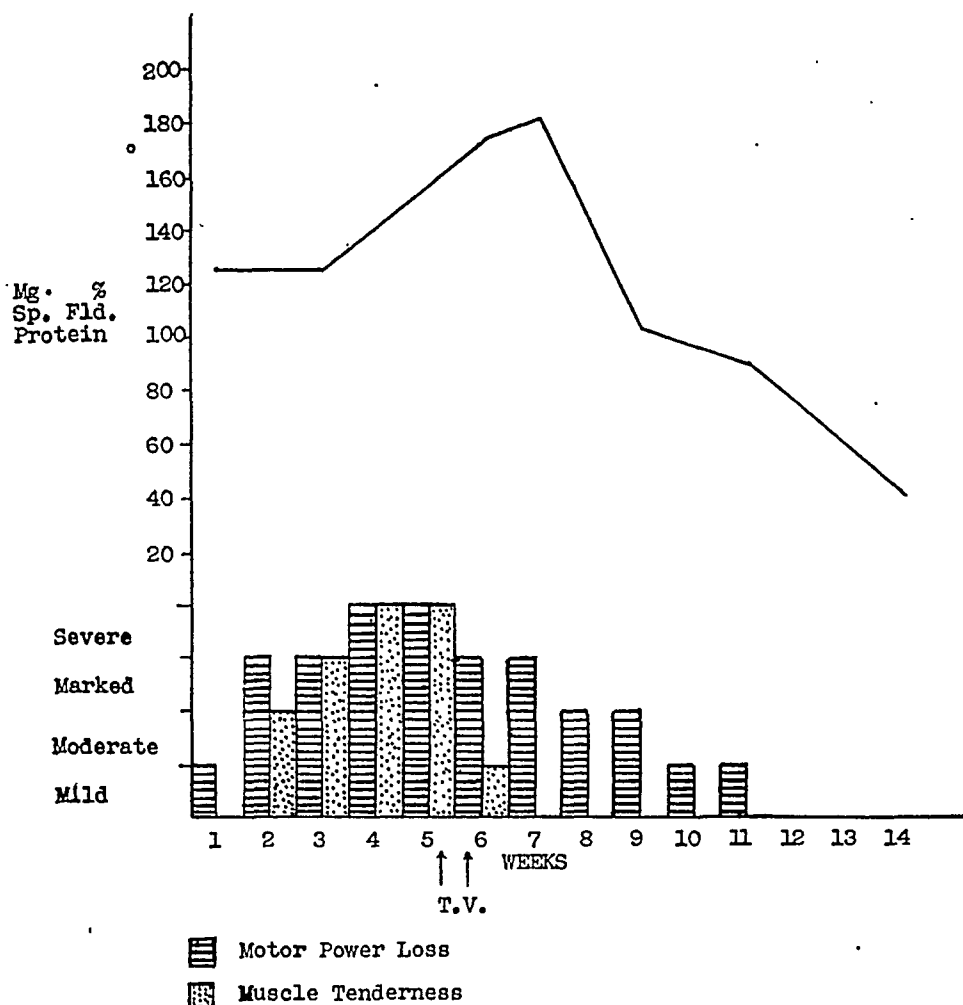


FIG. 1. Case 1. M. F.

was present. An unremitting downward progression was not affected by the usual supportive measures or vitamins, but recovery was initiated immediately after the institution of typhoid vaccine fever therapy.

*Case 2.* R. M., a garage attendant, aged 29, was admitted to the Neurologic Service on June 25, 1946, complaining of numbness, tingling and weakness of all extremities. Three weeks prior to admission he had a mild sore throat. One week later there ensued gradual tingling and numbness of the fingers and toes accompanied by weakness of the lower extremities, followed within two days by weakness in the upper extremities. This rapidly progressed to the stage where the patient could no longer kneel to lift a tire off a wheel. There was no excessive alcoholism, and the diet was adequate.

On admission the patient presented mild weakness of the upper and moderate weakness of the lower extremities, which were hypotonic, with absent tendon reflexes. Superficial sensory loss of a glove and stocking type was present, with position and vibration sense impaired in the lower extremities. The initial lumbar puncture was negative except for a faint Pandy reaction and a total protein of 49 mg. per cent. All laboratory studies, including throat cultures and Schick test, and urine studies for lead and porphyrins showed no abnormality.

The following four weeks, both motor and sensory disturbances advanced in severity and distribution, the former involving all the muscles of the trunk and ex-

tremities with atrophy of the forearms, hand muscles, thighs and calves. In addition, the patient developed hoarseness associated with weakness of the laryngeal abductors, some difficulty in swallowing, exquisite deep muscle tenderness, and occasional urinary incontinence which persisted despite intensive vitamin therapy.

Intravenous typhoid vaccine therapy was instituted on July 22. Six doses were given over a two week period, beginning with 10 million organisms and terminating with 100 million. Severe exacerbations of muscle pain were experienced with each temperature rise. Three days after inception of this therapy, the deep muscle tenderness was markedly diminished and was absent in 10 days. Urinary incontinence ceased. Motor power began to improve 18 days after beginning therapy and steadily improved, lagging mainly in movements of the ankles and toes. Sensory modalities improved within two weeks.

Upon discharge on August 12, there was minimal weakness in the extremities. Tendon reflexes were absent except for the biceps and triceps reflexes. Sensation was intact to pin prick and diminished to touch only over the toes, where position sense was also mildly impaired. Vibration remained impaired to the midtibial area. Follow-up examination two months later was completely negative neurologically but for impaired position sense in the toes and absent knee and ankle reflexes.

*Comment.* This case presented a severe peripheral neuropathy following an upper respiratory infection, with albumino-cytologic dissociation in all spinal fluid examinations except the first. There was an unremitting downward progression while on the usual supportive therapy. Fever induced with typhoid vaccine appeared to initiate an eventual complete recovery.

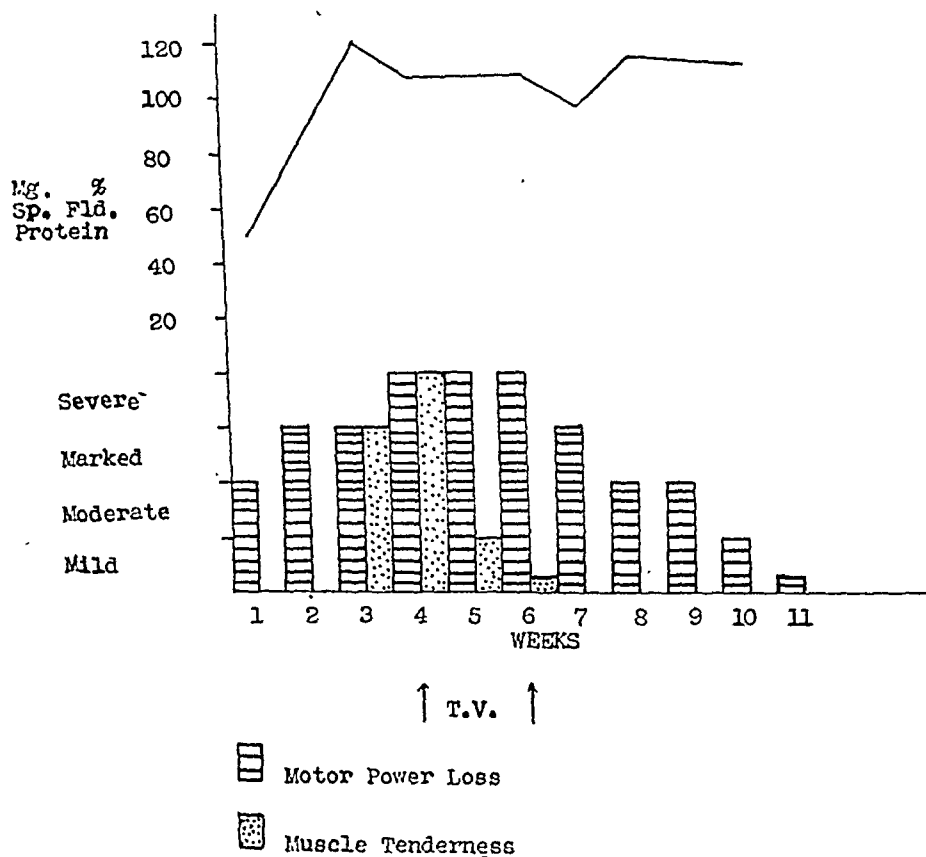


FIG. 2. Case 2. R. M.

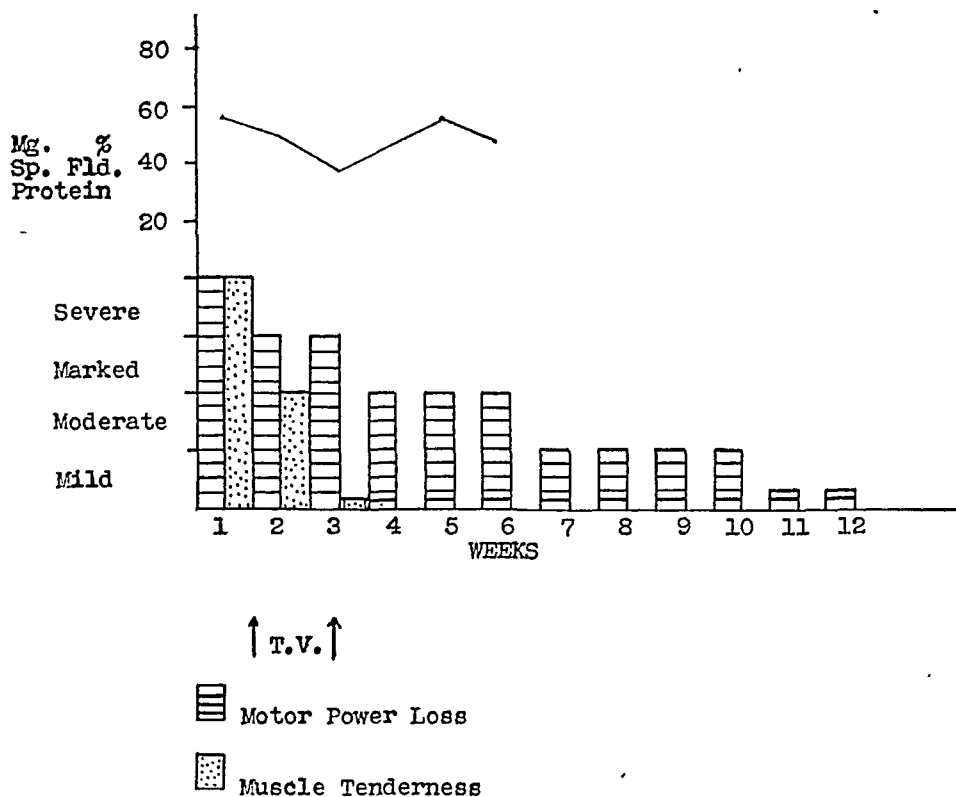


FIG. 3. Case 3. J. H.

*Case 3.* J. H., a restaurant counterman, aged 40, was admitted to the Neurologic Service on November 14, 1946, complaining of tingling and numbness in all extremities. On September 20 he had developed pustular lesions of the left side of the face, head and neck following receipt of a blow with a broomstick. He entered the Dermatologic Service of another hospital on September 30, where local treatment resulted in improvement. Eight days later he first noted pins and needles sensations in the fingers. Within three days there occurred weakness of the upper extremities which rapidly progressed to involve all extremities, with diminution of reflexes. This rapid decrease in power developed while on heavy vitamin therapy. There was a history of moderate alcoholism, but the diet was adequate.

On admission to our service the patient presented marked weakness of all the musculature, most severe distally with atrophy of the hand muscles. The tendon reflexes were diminished in the upper and lost in the lower extremities. There was severe calf tenderness and plantar hyperesthesia, a glove and stocking type of sensory diminution with hyperalgesia of the fingertips. Touch appreciation was absent in the hands and in the lower limbs up to the inguinal area. Position sense was absent in both fingers and toes, with vibration impaired in all extremities. An initial lumbar puncture was normal except for a total protein of 51 mg. per cent. All laboratory data were negative, including urinary porphyrin studies.

During the first week of observation motor weakness became more severe, and deep muscle tenderness was exquisite. Intravenous typhoid vaccine therapy was instituted on November 21. Four injections were given over a 10 day period, with an initial dose of 10 million organisms and a final dose of 80 million. With each dose, severe exacerbations of pain in all extremities occurred, the severity decreasing with successive doses. One day, following institution of therapy, the patient volunteered the information that he "felt one thousand per cent better," and objectively showed a

marked diminution in muscle tenderness and plantar hyperesthesia, with a complete disappearance of these findings 11 days later. Motor power began to improve four days after typhoid therapy was begun and continued to improve gradually, with the greatest lag in the hand muscles and movement of the ankle and toes, finally permitting satisfactory performance of routine tasks three weeks later. All sensory modalities also showed improvement during this time. Examination 10 weeks after beginning therapy revealed mild weakness of the extremities, more marked distally, mild hyperalgesia over the fingertips, patchy areas of hypesthesia and hypalgesia over hands and feet, impaired position sense in the fingers with absence persisting in the toes, and vibration impaired up to the ankles. Only the biceps and triceps reflexes were present.

*Comment.* This case presented a typical picture of a peripheral neuropathy with slight increase in the spinal fluid protein, preceded by an acute scalp infection of unknown etiology. There was no response to the usual supportive and vitamin therapy. Immediately after the institution of typhoid vaccine fever therapy, muscle pain and tenderness disappeared. The return of sensation and motor power was more gradual.

*Case 4.* G. G., a nurse, aged 31 years, entered the Neurologic Service for her fifth admission on May 30, 1946. She complained of fever, redness and swelling of the left side of the face and forehead associated with a severe burning, tingling pain and numbness of the right side of the tongue. Previous pertinent history elicited the following: Her first admission occurred in September 1942 after contracting an upper respiratory infection following receipt of pertussis vaccine at a children's summer camp, where an epidemic suggestive of pertussis had occurred. At that time, findings of drowsiness, headache, girdle sensations, radicular pains, urinary incontinence, diplopia, bilateral fifth nerve involvement, right seventh and twelfth nerve involvement, weakness of the right arm and leg, a positive Babinski reflex on the left, and a right hemianalgesia and hemianesthesia had led to a diagnosis of acute encephalomyelo-radiculitis. She had improved following receipt of typhoid vaccine fever therapy. During the succeeding four years, repeated exacerbations occurred following upper respiratory infections, with symptoms similar to those on the original admission, although not as widespread and often involving other parts of the nervous system. Hospitalization was necessary in July 1943, February 1944, and January 1945. During the 1944 admission, typhoid vaccine fever therapy was given with very rapid recovery and again in 1945 with less prompt recovery.

On the present admission, positive findings included diminished sensation to pin and touch on the right side of the tongue, hyperalgesia with spots of hypalgesia over the ulnar aspect of the right forearm, spotty hypalgesia over the back of the right calf and thigh and exquisite pain along the course of the right ulnar nerve. Typhoid vaccine was given two days after admission with a temperature rise to 105° F., but no relief from symptoms occurred. Because of the constant history of an upper respiratory infection preceding each exacerbation, the patient was studied from an allergic point of view. A histamine phosphate sensitivity test resulted in a severe flare and wheal, followed in 15 minutes by an exacerbation of burning, itching and swelling of the left side of the face and in 30 minutes by a generalized urticaria. Desensitization was attempted with intravenous histamine phosphate, but the original symptoms remained unimproved. At the insistence of the patient, typhoid vaccine therapy was again instituted on June 15, and following one injection all symptoms abruptly subsided, leaving the patient only with hypalgesia of the left cheek, right side of the tongue, and along the distribution of the right ulnar nerve. She was discharged on June 19 and has since been receiving 0.5 c.c. of 1:1000 histamine phosphate twice weekly. Up to December 1946, she has had only two mild upper respiratory infections without neurological exacerbations.

*Comment.* This case presented at the onset a picture of an acute encephalomyelo-radiculitis following an upper respiratory infection and receipt of pertussis vaccine. She continued to have exacerbations in spite of almost constant vitamin therapy. No form of treatment offered the patient any relief except fever induced with typhoid vaccine. Although this was not always effective, the patient would come to the hospital requesting it when her symptoms were severe. The possibility of an allergic factor is suggested by her severe reaction to a histamine phosphate sensitivity test.

*Case 5.* M. S., a clerical worker, aged 35 years, who had also worked as a painter on and off for 15 years, entered the Neurologic Service on April 16, 1946, complaining of fever, attacks of hiccough and vomiting, radiating pains, and obstipation. Four months previously he had developed severe, intermittent, lancinating pain in the right lower back, which disappeared spontaneously in four days. Three months later similar pain developed in the left elbow, radiating down into the fourth and fifth fingers. In three weeks, it also occurred in the anterior left chest, and shortly thereafter in the anterolateral aspect of the right leg. No bowel movement had occurred for five days prior to admission, and hiccough and vomiting had begun two days before entry. There was no antecedent acute infection, no alcoholic history, and the diet was adequate.

On admission, the temperature was 101° F., the patient appeared acutely ill and was subject to bouts of hiccoughing and vomiting. The pains in the above described areas were of such exquisite intensity that bedsheets had to be kept away from the body by a cradle, and superficial sensation could be tested only with a cotton tip. The zones most severely involved were C4 to T4 and L1 to L2 on the left; less severely involved root zones were S1 to S3 on the left, and L2 to L3 on the right. Position sense was impaired in the left big toe, and vibration caused a burning dysesthesia in all extremities. There was mild hyperesthesia over the right side of the face. Slight paresis of the right lower extremity and marked paresis of the left lower extremity were present. The tendon reflexes were all hyperactive except for diminished triceps responses. The superficial abdominal reflexes were absent on the left and diminished in the right upper quadrant. An initial spinal puncture revealed a pressure of 240 mm. of water, but was otherwise negative. All subsequent lumbar punctures were negative except for a slight positive Pandy reaction on two occasions. Virus studies of the spinal fluid were negative. All laboratory data were within normal limits.

Two days after admission severe spasms of the calf muscles occurred. In spite of this development, the hiccoughing and vomiting receded and radicular pains lessened during the first week. Motor power began to improve in three and a half weeks. During the sixth week of hospital stay, further violent muscle spasms occurred, involving a greater amount of the musculature than previously. A Babinski and a Chaddock sign developed on the left. During the ninth week an episode of blurred vision occurred for half an hour. This was repeated a week later, but persisted, and a horizontal nystagmus was also present. Atrophy of the left hypothalamic eminence with occasional fibrillations was noted. During the tenth week the bouts of hiccough and vomiting recurred, and the patient complained of numbness of the left side of the face. A complete left sided hypesthesia, hypalgesia and thermhypesthesia was found, most marked from T10 to C4. The right pupil was smaller than the left. There were bilateral positive Babinski signs.

On July 14 intravenous typhoid vaccine therapy was begun. A total of five injections over a 12 day period was given, starting with 10 million organisms and terminating with 200 million. One day after this therapy was begun the patient showed subjective improvement and lessened frequency of muscle spasms. Superficial sensation on that day was normal except for mild hyperesthesia of the right

side of the face and ulnar aspect of the left palm. These were the most minimal sensory disturbances since the patient's admission. A gradual recovery of motor power was evident shortly after this therapy and continued until the patient signed his release on August 3. On that day the residual findings were a coarse horizontal nystagmus on forward gaze, mild hyperesthesia of the right side of the face and ulnar aspect of the left palm, minimal paresis of the left lower extremity, generally hyperactive reflexes except for the triceps, absent abdominal reflexes, and occasional bilateral positive Babinski signs. Position sense was impaired in both big toes and vibration sense was diminished bilaterally up to the iliac crests.

*Comment.* This case presented an acute encephalo-myo-radculitis with consistently normal spinal fluid. Although there were periods of recession of symptoms, exacerbations were characterized by increasing sensory involvement and a greater amount of musculature involved in the spasms which so distressed the patient. We believe that the improvement following typhoid vaccine fever therapy was too prompt and sustained to be purely coincidental, although we hesitate completely to attribute the patient's partial recovery to this form of therapy.

*Case 6.* E. J., a housewife, aged 52 years, entered the Neurologic Service on December 5, 1946. On December 2 she had awakened from sleep with wheezing and tightness in the chest. Within 12 hours, vertigo, severe suboccipital headache, anorexia and generalized weakness ensued. On December 3, she could not close either eye, and the right side of her face felt "drawn up." This was followed by pins and needles sensations in all extremities and knifelike pain in the upper back, radiating anteriorly to the chest and abdomen. Paresis of both legs followed, then difficulty in starting the urinary stream, and finally transient diplopia.

On admission she presented a facial diplegia, moderate paresis of extension of both arms and weakness of both lower extremities. The tendon reflexes were absent except for a left biceps response, and a right positive Babinski with an equivocal left Babinski was noted. *Cerebellar ataxia on the right finger to nose test* was found. Superficial sensation was diminished below T6, most marked from the knees down. Sensation was also disturbed in both hands. Position sense was absent in both big toes, with vibration appreciation impaired to the costal margins. The patient spoke in a slurred manner and had difficulty in swallowing, although movement of the uvula and palate was normal. The initial lumbar puncture revealed a two plus Pandy reaction, two lymphocytes, and 77 mg. per cent of total protein. The white blood cell count was 14,000 with a normal differential. All other laboratory data were normal.

The patient became progressively worse, with more generalized shooting pains, increasing weakness, and transient periods of urinary retention followed by incontinence of both feces and urine. Bilateral fifth nerve disturbance developed, while deep muscle tenderness and plantar hyperesthesia became severe. Intravenous typhoid vaccine therapy was instituted on December 14, with an initial dose of 10 million organisms requiring a stepup dose of an additional amount because of a poor temperature response. Three injections over a five day period were given, with a final dose of 50 million organisms. On December 15, one day after this therapy was begun, the patient stated she had marked relief from her girdle pains and that she had not felt as well since the onset of her illness. She could now control rectal functions. The sensory level showed a sudden drop to T12, below which it was much less marked than on admission. Motor power and calf muscle tenderness remained unchanged, but there was no further progression of paresis. Two days later there was definite improvement of power in the distal musculature of the lower extremities. However, on December 18 calf muscle tenderness became more severe and an exacerbation of radicular pains occurred. On December 20 the patient was found in shock and died in a few hours. Autopsy revealed an aspiration pneumonia with atelectasis.

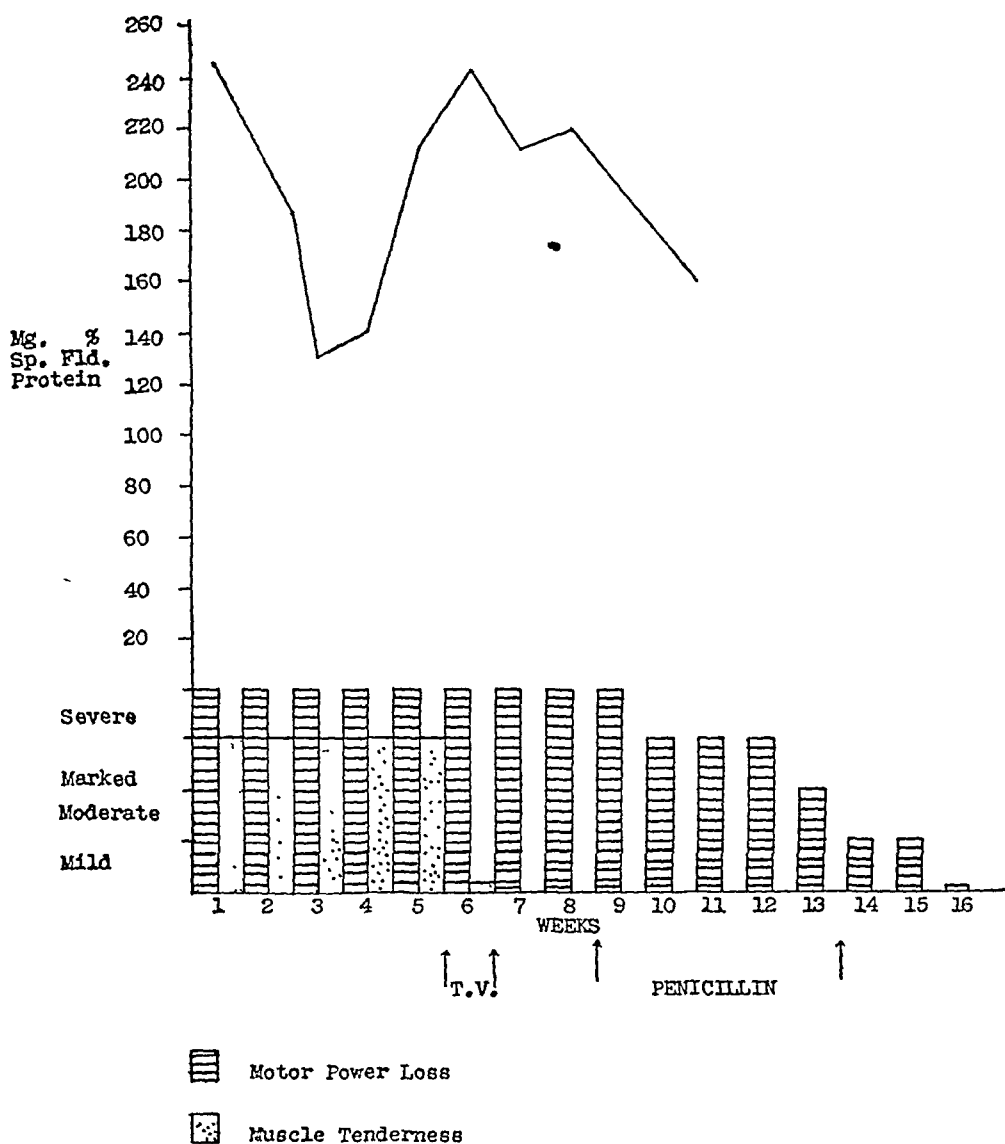


FIG. 4. Case 7. R. Mn.

*Comment.* The unfortunate sudden death of this patient, who presented signs of an encephalo-myelo-radiculo-neuritis, prevents any accurate evaluation of her response to typhoid vaccine fever therapy. There was definite recession of the sensory level from T6 to T12 and arrest of fecal incontinence within 24 hours after beginning the fever therapy.

*Case 7.* R. Mn., a drifter, aged 39 years, entered the Neurologic Service on October 15, 1946, complaining of weakness and muscle aching. Five weeks previously he had chills and fever for several days, followed in one week by burning sensations in the soles of the feet and weakness of the ankles. Thereafter, progressive involvement of all the muscles and cramping pains in the calves developed. Up to four months prior to hospital entry, he had been a heavy drinker with a poor dietary intake.

On admission, he appeared chronically ill. The lingual and cutaneous changes suggested avitaminosis. The pupils were irregular, unequal and reacted poorly to light. Severe weakness of all the muscles, with partial wrist and foot drop, was

noted. Only a left triceps reflex was elicited, a glove and stocking type of hypalgesia and hypesthesia was present, most marked distally, with vibratory appreciation absent up to the elbows and position sense absent in the fingers and toes. Laboratory data revealed a mild secondary anemia, an increased sedimentation rate, with urinalyses negative for lead and porphyrins. The spinal fluid was under normal pressure, with five polymorphonuclear leukocytes and five lymphocytes, a total protein of 254 mg. per cent, sugar 76 mg. per cent, and chlorides 704 mg. per cent. The colloidal gold curve was 4454332100, and both blood and spinal fluid Wassermann reactions were four plus.

Heavy vitamin therapy for one month resulted only in the improvement of the patient's sense of general well being. Repeated spinal fluid studies showed a rising cell count up to 65 lymphocytes and a decrease in total protein to 133 mg. per cent. Intravenous typhoid vaccine therapy was instituted on November 19. Four injections were given over an eight day period, beginning with 10 million organisms and terminating with 80 million. With each paroxysm of fever, a severe exacerbation of calf muscle tenderness occurred, diminishing in intensity with each successive dose.

On the day following the first injection, the patient felt subjectively better with complete disappearance of deep muscle tenderness. The only other improvement was somewhat less extensive glove and stocking sensory disturbance. Laboratory data indicated syphilis as at least co-existent with the presenting disturbance, and penicillin therapy was instituted on December 15, the patient receiving 50,000 units intramuscularly every three hours. One week later, after having received two and a half million units (and one month after the fever therapy was begun), the patient showed a surprising sudden improvement. Motor power had increased throughout, even in the hand muscles and at the ankles and toes. By December 24 there was no longer any wrist drop, and the patient had improved. He could now wash and feed himself. The glove and stocking distribution of sensory loss had diminished markedly, with touch now perceived, although diminished, over the hands, absent in the feet, and diminished to the knees. By mid-January he was walking about the ward with slight support. The tendon reflexes were still absent. Pin and touch sensation were unimpaired in the upper extremities and only mildly impaired in the lower extremities up to the ankles. Position sense was present in the fingers but impaired in the toes. Vibratory appreciation was intact.

*Comment.* This patient presented a severe peripheral neuropathy, with increased cells and protein in the spinal fluid. This illness followed a febrile episode but was complicated by the presence of neurosyphilis. Supportive therapy offered no relief, but immediately following typhoid vaccine therapy pain and muscle tenderness disappeared. Return of motor power was delayed until after the administration of penicillin. Evaluation of the effect of the latter therapy on the course of recovery is difficult because of the short interval between the beginning of its administration and the return of motor power.

## DISCUSSION

This report is limited to an evaluation of the use of fever therapy induced by the intravenous injection of typhoid vaccine in cases which can best be included under the general classification of acute infectious neuronitis or neuronopathy. TAB vaccine was used, but only the number of typhoid organisms was counted. The dosage schedule depended upon the febrile response and clinical reaction of the patient. The initial dose was 10 million organisms. If little or no response was obtained to the first dose, a stepup dose of the same amount was given within a few hours. Increasingly larger



doses were given every second to third day, and on intervening days salt, fluids and plasma were given as indicated. Febrile responses varied from  $101^{\circ}$  to  $105^{\circ}$  F. A consistent response in all patients except Case 5 was severe exacerbations of pain in the extremities during the febrile phase. So constant was this finding that it seemed to indicate that an effect was being obtained, and treatment was discontinued when it no longer occurred. In spite of the extreme discomfort of the patients during the treatment, their relief from pain was so gratifying that they themselves often requested further injections.

Not infrequently, in similar cases, spontaneous recovery after varying intervals of time is observed and, therefore, conclusions as to any form of therapy can by no means be dogmatic and absolute. However, among the cases observed on our Neurologic Service, we sought to choose only those whose course appeared to be constantly downward in spite of all the usual supportive therapy. Cases 1, 2, 3, 6, and 7 showed increasing muscle tenderness, loss of motor power and sensory diminution. Case 4 had repeated exacerbations over a four year period. Case 5 showed progressive involvement of the musculature in severe spasms, and marked advance in sensory disturbance.

Of the seven patients, six improved following typhoid vaccine fever therapy. Case 6 died before reliable evaluation was possible, the cause of death being aspiration pneumonia with atelectasis. Case 7 showed rather late improvement after the fever therapy but too rapid improvement after penicillin therapy to attribute it entirely to the latter drug. The nature of the improvement is considered in four categories.

(a) *Relief of Pain.* This was the most dramatic feature of the therapy. The muscle tenderness was reduced to a minimum within 24 to 48 hours after the first injection, was usually completely absent within a week, and did not recur. Once the pain was relieved, the patients would acquire a sense of well being and give up their usually pessimistic attitude toward their illness. The relief from pain and tenderness also permitted the earlier institution of physiotherapeutic procedures.

(b) *Recovery of Motor Power.* This lagged behind the relief of pain and was present in cases 1, 2, 3, and 4. The return of power in case 5 following vaccine therapy was no greater or more rapid than it had been during previous remissions, although it was maintained much longer. Case 6 died before accurate evaluation was possible, but the advancement of paresis appeared to have ceased following typhoid vaccine. Case 7 showed recovery of motor power beginning 30 days after vaccine therapy was instituted and seven days after penicillin was begun.

(c) *Recovery of Sensation.* Sensory recovery following typhoid vaccine therapy was inconstant and variable and usually the last to respond, except in cases 5 and 6. Case 5 displayed a return of sensation following the first injection of typhoid vaccine that was as dramatic as the relief of pain in the other cases. Case 6, who had a sensory level at T6, showed a

regression of this level to T12 almost immediately. In most of the patients a return of superficial sensation was heralded by the appearance of patchy areas of hyperesthesia and hyperalgesia in the previously involved areas, but these were never very disturbing to the patient.

(d) *Spinal Fluid Changes.* No correlation existed between the severity of the illness, the downward course and the final recovery on the one hand, and the spinal fluid protein on the other. Case 5 had a normal spinal fluid throughout. Case 4 showed normal spinal fluids from 1942 to 1946. Case 1 showed decreasing spinal fluid protein during recovery, whereas cases 2, 3, and 7 maintained a high spinal fluid protein even during the recovery phase.

The basis of the favorable response to fever induced with typhoid vaccine remains obscure. The numerous explanations offered are an indication of the lack of positive evidence as to exactly what occurs. It has been suggested that the elevated body temperature creates an unfavorable environment for the pathogenic organism concerned. This does not seem likely in several of our cases where a good response was noted with only a minimal rise in temperature. Other speculations concern themselves with the blood supply, implying that an increased vascular flow occurs peripherally in inflamed areas, increasing oxidation and nutrition, furthering dilution of toxins and healing of inflamed tissue. Still a third suggestion concerns itself with the body's general cellular and glandular responses because of leukocytosis, phagocytosis and enhanced antibody formation, all resulting in a better mobilization of the entire system of tissue defense.

### SUMMARY

1. Seven cases of acute infectious neuronitis or neuronopathy have been presented and their response to fever induced by typhoid vaccine evaluated.
2. The method of typhoid vaccine fever therapy has been outlined.

### CONCLUSIONS

The favorable response of six of seven patients to typhoid vaccine fever therapy indicates that further intensive trial with this form of therapy in acute infectious neuronitis or neuronopathy is indicated.

### BIBLIOGRAPHY

1. OSLER, W.: The principles and practice of medicine, 1892, D. Appleton and Co., New York, 1077 pp.
2. MILLS, C. K.: The reclassification of some organic nervous diseases on the basis of the neuron, Jr. Am. Med. Assoc., 1898, xxxi, 11.
3. GUILLAIN, G., BARRÉ, J. A., and STROHL, A.: Sur un syndrome de radiculo-nevrite avec hyperalbuminose du liquid cephalo-rachien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, xl, 1642.
4. BRADFORD, J. R., BASHFORD, E. F., and WILSON, J. A.: Acute infective polyneuritis, Quart. Jr. Med., 1918, xii, 88.

5. GILPIN, S. F., MOERSCH, F. P., and KERNOHAN, J. W.: Polyneuritis, a clinical and pathological study of cases frequently referred to as instances of neuronitis, *Arch. Neurol. and Psychiat.*, 1936, xxxv, 937.
6. FORSTER, F. M., BROWN, M., and MERRITT, H. H.: Polyneuritis with facial diplegia, *New England Jr. Med.*, 1941, ccxxv, 51.
7. DEJONG, R. N.: The Guillain Barré syndrome, *Arch. Neurol. and Psychiat.*, 1940, xlv, 1044.
8. ROSEMAN, E., and ARING, C. D.: Infective polyneuritis, *Medicine*, 1941, xx, 463.
9. STRAUSS, I., and RABINER, A. M.: Myeloradiculitis: a clinical syndrome with report of seven cases, *Arch. Neurol. and Psychiat.*, 1930, xxiii, 240.
10. MACKAY, R. P.: Acute encephalomyeloradiculitis, *Med. Clin. N. Am.*, 1945, xxviii, 1.
11. BENNETT, A. E.: Horse serum neuritis, *Jr. Am. Med. Assoc.*, 1939, cxii, 590.
12. SCHNEIDER, D. E.: Acute infectious meningo-myelo-radiculitis, *Jr. Mt. Sinai Hosp.*, 1934, i, 173.
13. KESCHNER, M.: A case of encephalo-myelo-radiculitis, *Jr. Mt. Sinai Hosp.*, 1935, i, 123.

# PRIMARY SPLENIC NEUTROPENIA WITH ARTHRITIS (SO-CALLED FELTY'S SYNDROME). ITS TREATMENT BY SPLENECTOMY \*

By SOL SMITH, M.D., and E. S. McCABE, M.D., *Baltimore, Maryland*

IN 1924 Felty<sup>1</sup> described the syndrome of chronic rheumatoid arthritis associated with splenomegaly and leukopenia. He was preceded by Still<sup>2</sup> who, in 1897, reported a disease of children characterized by chronic joint disease, splenomegaly and leukocytosis. In 1932 Hanrahan and Miller<sup>3</sup> performed the first splenectomy for Felty's syndrome. The operation was done primarily to relieve the patient of the discomforts of the enlarged spleen and to correct the leukopenia. What reasoning led them to expect the latter is obscure. Because of the good result obtained by Hanrahan and Miller, Craven<sup>4</sup> carried out the same operation in his patient in 1934. However, it remained for Steinberg<sup>5</sup> in 1942 to note for the first time the bone marrow hyperplasia in two such cases and to suggest that the spleen might be inhibiting the maturation of the granulocytes. He further stated that "if inactivity of the bone marrow is present splenectomy should not be done."

In 1939 Doan and Wiseman<sup>6</sup> reported three cases of "a newly recognized granulocytopenic syndrome with the bone marrow showing myeloid hyperplasia of qualitatively normal cells." Splenomegaly and profound leukopenia were present. There was no evidence of liver disease, chronic infection or other factors that might produce this picture. None had any recognizable arthritis. All of these patients were cured by splenectomy, and there was a prompt reestablishment of a normal peripheral leukocyte count. The spleens all showed histologically excessive phagocytosis of the granulocytes.

In 1939 Moore and Bierbaum<sup>7</sup> and in 1941 Muether et al.<sup>8</sup> reported two more such cases which were cured by splenectomy. Doan and Wiseman<sup>9</sup> in 1942 added two more cases to their original group and named the syndrome primary splenic neutropenia. They compared it to congenital hemolytic icterus and essential thrombocytopenic purpura. They stated that all of their cases have the "common denominator" of profound granulocytopenia, panhyperplasia of the bone marrow, enlarged spleen, and cure by splenectomy. In addition there were also present varying degrees of anemia and thrombocytopenia which were asymptomatic and which were coincidentally corrected by removal of the spleen. These investigators felt that a single mechanism was responsible for the varying degrees of anemia, neutropenia and thrombocytopenia in this group of cases. The spleens all showed excessive phagocytosis of granulocytes, red cells and platelets. They concluded that the syndrome is due to a "hypersplenism" in which there is an

\* Received for publication November 15, 1946.

From the Medical Service, Mercy Hospital, Baltimore, Md., and the Department of Medicine, University of Maryland, Baltimore, Md.

accentuation of the physiologic function of disposing of blood cells and that it is comparable to congenital hemolytic icterus and essential thrombocytopenic purpura. In the former disease the phagocytic activity of the spleen is directed chiefly against the red blood cells; in the latter, chiefly against the platelets; and in the neutropenic syndrome chiefly against the granulocytes.

Furthermore, Doan and Wiseman did not believe that Felty's syndrome could be either included or excluded from this neutropenic syndrome because of the limited data available.

In 1945 these same investigators<sup>10</sup> first used the term splenic panhematopenia for the picture in which the enlarged spleen is associated with a marked and usually symptomatic decrease in all the cellular elements of the blood. They described several such cases. They felt that in this syndrome the spleen fails to discriminate between the blood cells passing through it, and that there results a peripheral blood picture and clinical picture resembling the complete marrow hypoplasia seen in aplastic anemia. In these cases the bone marrow showed hyperplasia of all the normal elements without pathological maturation arrest or significant qualitative abnormalities. These patients were also cured by splenectomy.

With this background in mind we wish to present two cases showing chronic neutropenia, splenomegaly and advanced arthritis. The first case showed a hypoplastic bone marrow, some anemia and thrombocytopenia, and the second a hyperplastic bone marrow with no anemia or thrombocytopenia. Splenectomy was followed in both by a return of the blood pictures to normal and marked clinical improvement in the patients' health.

#### CASE REPORTS

*Case 1.* W. C. T., a white male of 52, salesman, was treated at another local hospital in February 1941 for pneumonia of the right middle lobe. In addition to the pulmonary changes, examination revealed enlargement of the spleen, anemia and leukopenia (table 1). The pneumonia cleared up on sulfapyridine therapy, but the anemia, splenomegaly and leukopenia persisted. Diagnoses on discharge were pneumonia and splenomegaly with blood dyscrasia (unexplained).

On May 10, 1946 we first saw the patient when he was admitted to the Mercy Hospital because of weakness and loss of 15 pounds since January 1946. He stated that "everything I do is an effort and I always feel as if I needed sleep."

Past history revealed repeated infections. In 1909 he was hospitalized for nine months for pulmonary tuberculosis. Chronic rheumatoid arthritis had been present since 1921. He had had gonorrhea twice, the last time about 1930. Cellulitis of the dorsum of the left foot occurred in 1936. He had had pneumonia in 1941, pleurisy in 1942, and pneumonia again in December 1945. There had been no exposure to any drugs or chemicals.

Examination revealed an elderly looking, gray-haired man appearing older than his stated age and weighing 143 pounds. He was somewhat pale, with dark brown pigmented macular areas around the ankles and extending a short distance up both legs. There was complete adentia (artificial plates). The heart and lungs were negative. The blood pressure was 105 mm. Hg systolic and 90 mm. diastolic. The

TABLE I

[illegible]

spleen was enlarged, extending to the umbilicus. There was no enlargement of the liver, no ascites, and no evidence of collateral circulation. There were marked arthritic deformities of the wrists and of the fingers of both hands, with ulnar deviation, and moderate changes in the knee joints.

Roentgenographic studies of the chest and gastrointestinal tract were negative. No esophageal varices could be demonstrated. Roentgenograms of the joints showed extensive rheumatoid changes of the bones of the hands and wrists and minimal changes in the knees. The electrocardiogram was normal.

TABLE II

Sternal Marrow of Case 1 in Comparison with Steinberg's <sup>5</sup> Hyperplastic Marrow and Normal Marrow from Wintrobe

	May 14	June 27	July 9	Steinberg	Wintrobe
Myeloblasts	0.0	0.6	0.0	7.0	2.0
Promyelocytes	0.2	1.8	1.0	9.0	5.0
Myelocytes	4.2	5.8	2.8	10.0	12.0
Juveniles	6.0	8.8	5.0	7.0	22.0
Staff	16.6	16.8	21.2	8.0	
Polym. Neut.	7.4	5.0	33.4	12.0	20.0
Polym. Eosin.	2.4	1.0	4.4	1.0	2.0
Polym. Basoph.	0.0	0.0	0.0	0.0	0.2
Prolymphocytes	0.6	1.8	0.4	8.0	
Lymphocytes	22.0	33.0	24.0	6.0	10.0
Monocyte	1.2	0.4	2.0	2.0	2.0
Megaloblast	1.6	0.0	0.2	3.0	
Erythroblasts	8.6	7.6	1.0	9.0	4.0
Normoblasts	28.6	16.6	4.4	16.0	18.0
Tissue cells	0.6	0.8	0.2		0.2
Megakaryocytes		0.2			0.4
Plasma cells				2.0	0.4
Comment:—Hypocellular, granulo- penic but normo- blastic.		After folic acid.	Post op. granulo- cytes in- creased.	Hyper- plastic.	Normal.

The successive blood counts are presented in table 1 and the bone marrow studies in table 2. Other laboratory data were as follows: gastric analysis showed relative hypochlorhydria with a prolonged rise, serum proteins 8.1 per cent, albumin 4.1 per cent, globulin 4.0 per cent, vitamin C level 0.7 mg. per cent, cephalin flocculation 2 plus in 48 hours, prothrombin clotting time (undil.) 19 seconds, (dil.) 67 seconds, icteric index 5.2, van den Bergh 0.5 mg. Blood sugar and urea were normal. Serologic test for syphilis was negative. Bromsulfalein test of liver function showed 4 per cent retention in 60 minutes. Hematocrit 38 per cent, clot retraction was complete in 12 hours, bleeding time was one minute, coagulation time was 10 min. 32 sec. Gothlin index normal, urine contained 0 to 2 plus albumin, no sugar; urobilinogen was present.

The bone marrow studies (table 2) were interpreted by Dr. H. R. Peters, hospital hematologist, as follows: preoperative marrow, May 14, 1946, "normoblastic marrow in the sense that in this relatively hypocellular marrow the normoblasts are actually increased. It is not a hyperplastic marrow. No abnormal cells are seen. Would be compatible with any leukopenic blood dyscrasia, primary splenic neutropenia, so-called Felty's syndrome, Hodgkin's of the spleen, etc."

There was no change in the patient's condition or blood picture during this first Mercy Hospital admission. He was discharged on May 19 after nine days in the hospital, and at this time began to take folic acid 5 mg. four times daily which he continued to take until June 24, 1946, the day of the second hospital admission. Blood counts were made several times weekly while on this medication, except for a lapse of one entire week. As shown in tables 1 and 2 the main features of the blood and bone marrow studies were the presence of a marked leukopenia and granulocytopenia, a moderate anemia and thrombocytopenia, and a hypoplastic bone marrow.

On readmission to the hospital the most relevant blood studies were repeated, together with another sternal puncture to see what effects, if any, folic acid had produced. No change was noted in the blood picture except a moderate increase in the number of platelets.

On June 29, 1946 a splenectomy was performed by Dr. Walter D. Wise. At the operation the liver appeared grossly normal and the splenic artery and vein were much dilated. The splenic vein was not thrombosed. The spleen weighed 1446 grams, measured 8.5 by 6 by 3.5 inches, and was fairly soft. Smears taken from the pulp of the freshly removed spleen and stained with Wright's stain showed no unusual phagocytosis (supravital stains not made).

Microscopic description of the spleen by Dr. Walter C. Merkel, hospital pathologist, was as follows: "The malpighian bodies are well preserved, the germinal follicles are hypertrophied. The sinusoids are markedly dilated and engorged with red cells. The reticulum is reinforced by fibroblasts; there is no patchy fibrosis. There is a moderate amount of free pigment; an occasional large phagocytic cell is encountered which also contains pigment. There are no polys; the predominating cells are lymphocytes. Plasma cells are relatively numerous. The capsule is thickened, trabeculations are hypertrophied. There is no hemorrhage, no infarction, and no accumulation of pathological leukocytes. There is nothing to suggest neoplasm." Pathological Diagnosis: Splenomegaly characterized by hypertrophy of malpighian bodies and hyperemia. Compatible with Felty's syndrome. The conditions which can be ruled out are Hodgkin's, Banti's syndrome, and the leukemias.

The adrenalin test done before splenectomy showed an increase in the leukocytes from 1600 to 2200 with no change in per cent of granulocytes. Postoperative marrow July 5, 1946 (table 2): "Marrow still grossly hypoplastic. The only change from previous smear is a slight increase in granulocytes. The erythroblastic elements are proportionately less than before splenectomy."

The patient withstood the operation well and was discharged 17 days later. The improvement in his blood count is shown in table 1. He was last seen on November 14, 1946 at which time he had gained 20 pounds in weight and stated that he felt stronger, had more pep, and was able to do much more work than he had done for years.

*Case 2.* This patient, a 59 year old white female, was first seen by her family doctor about March 15, 1945, complaining of an ulcer on the lateral aspect of her left ankle which had been present for six months. In addition she also had symptoms and signs of arthritis in both shoulders, elbows and knees, which she stated had been present for four years. Attention was directed primarily to the ulcer which was treated with Unna's paste bandage, tyrothricin and warm compresses at different times for three weeks without success. A complete examination then revealed an enlarged spleen and a low leukocyte count (table 3), and the patient was admitted to the Mercy Hospital on April 14, 1945 for further study.

In the hospital, in addition to the leg ulcer and the arthritis, the patient complained of general malaise, anorexia, fatigue and soreness of the tongue. There had been a loss of 75 pounds since the onset of the arthritis. The past history revealed



TABLE III

Date	Hgb		R.B.C.	W.B.C.	Stab.	Seg.	Lymph.	Mono.	Eos.	Platelet	Ict. Index	Van den Bergh	Fragility
	%	gm.											
4-7-45	82	11.8	4,990	2,500		10	56	9	22				
4-13-45				1,850	10	7	47	6	30				
4-16-45	87	13.7	4,800	1,800	2	10	58	2	28	556,800	10	0.4	
4-18-45				1,400	2	8	56	2	32			Indirect	
4-23-45	85	12.9	4.12	1,500	2	10	58	2	28				0.4
5-2-45	86	13.0	4.45	1,500	2	14	54	2	28				0.25
5-9-45	97	14.7	4.65	1,400	6	14	60	6	14				
Post-op.													
5-23-45	97	14.6	4.83	11,050	32	29	37		2	589,000			
5-24-45				11,150	42	34	20	2	2				
5-25-45				7,600	16	33	24	7	20				
5-26-45				8,200	12	9	25	1	53				
5-28-45	92	13	4.47	5,050	14	28	26	1	31	713,200			
6-2-45	96	14.5	4.63							1,259,600			
6-4-45				6,400	11	19	36		34				
6-5-45	90	13.6	4.70							1,205,760			
6-7-45				6,900	13	8	27	12	40				
6-12-45	90	13.6	4.7	6,100	11	7	46	30	6	989,100			
6-14-45	90	13.6	4.7										
8-5-45	96	14.5	4.35	13,800		68	26		6				

pneumonia and influenza in 1919. Menopause began at 53. There had been 13 pregnancies but several of these had miscarried. Family history was noncontributory.

Physical examination showed evidence of much weight loss, the weight at this time being 138 pounds. Small topi were present in the left ear lobe, lenticular opacities in both eyes, and artificial plates in both jaws. There was slight cervical adenopathy. Blood pressure was 122 mm. Hg systolic and 72 mm. diastolic. The heart and lungs were normal. The spleen was felt 3 cm. below the left costal margin. The liver could not be felt. Many subcutaneous, pea to olive size nodules were palpated over the different joints. On the lateral aspect of the left ankle there was an ulcer the size of a half dollar covered by a thin crust. The skeletal system showed marked kyphosis of the thoracic portion of the spine with arthritic deformities of the toes and fingers. Crepitus was present in both shoulders. There was marked limitation of motion of all the larger joints, with flexion deformity of the elbows and hands.

Roentgenograms of both hands showed atrophy of the bones and some soft tissue swelling around several interphalangeal joints. Roentgenograms of the dorsal spine revealed postural deformity with hypertrophic arthritis.

Study of the blood presented essentially a persistent granulocytic leukopenia with a marked eosinophilia (table 3). Bone marrow smears from sternal puncture showed an increase in the young granulocytes (hyperplasia) and an increase in the eosinophiles of all stages of maturity (table 4). Interpretation by Dr. H. R. Peters, hospital hematologist, was that it was not a "leukemic marrow, even a so-called eosinophilic leukemia."

Other laboratory data were as follows: urine was negative; total protein 5.9 per cent, albumin 3.4 per cent, globulin 2.5 per cent, albumin-globulin ratio 1.3; blood sugar 83 mg. per cent, urea 18 mg. per cent, uric acid 2.4 and 4.0 mg. per cent; hippuric acid 86 per cent excretion, bromsulfalein liver function 3.2 per cent retention in

TABLE IV  
Sternal Marrow, Case 2

Blast		6.2%
Myeloblast		
Premyelocytes	Neutrophilic	7.4%
	Eosinophilic	5.4%
Myelocytes	Neutrophilic	12.2%
	Eosinophilic	5.2%
	Basophilic	
Juvenile		12.6%
Staff		9.2%
Polymorphonuclears:	Neutrophilic	2.2%
	Eosinophilic	10.0%
	Basophilic	
Prolymphocytes		
Lymphocytes		12.4%
Megakaryocytes		
Plasmocytes		
Megaloblasts		
Erythroblasts		10.8%
Normoblasts		5.2%
Mitotic figures		0.4%
Unclassified		0.6%
Tissue cells		0.2%

Comment: Increase in immature myeloid cells with decrease in mature myeloid cells.

60 minutes; cephalin flocculation 4 plus in 24 hours. van den Bergh indirect reaction 0.4 mg. per cent; icteric index 10. Serologic test for syphilis was negative.

Biopsy of one of the subcutaneous nodules taken from over the olecranon process showed "necrosis, scarring and probable foreign body reaction, with no evidence of trichinosis."

Because of the leukopenia, enlarged spleen, and the evidence of hyperplasia in the bone marrow it was decided that splenectomy should be done, and accordingly operation was performed on May 22, 1945 by Dr. Patrick Phelan.

The spleen measured 18 by 11 by 6 cm. and weighed 600 grams. It was soft. Microscopically (C. G. Warner, Hospital Pathologist) the capsule was found to be thickened, the malpighian bodies were small and numerous and the pulp appeared both cellular and fibrous. It showed a rather non-specific histopathological picture, that is, "it is compatible with a number of different entities, and the diagnosis is not evident on histopathological examination alone."

The patient withstood the operation well. Blood counts subsequently showed a return to normal of the total number of leukocytes, but the eosinophilia persisted (see table 3). On June 16, 1945 the patient was discharged and was never seen again by us, having returned to her home in Tennessee.

On August 24, 1946, we received the following communication from her physician, Dr. P. J. O'Brien in LaFollette, Tenn. "The patient weighs 155 pounds, is ambulatory and still complains of her arthritis but not so much as previously. The ulcer on her ankle, although still present, is smaller, about the size of a quarter, with smooth edges. Her blood count is: hemoglobin 95 per cent, red blood cells 4,350,000, white blood cells 13,000, polymorphonuclear leukocytes 64, large lymphocytes 10, small lymphocytes 12, basophiles 8, eosinophiles 6. Platelet count was not done. From her history I think she has made a marked improvement."

## DISCUSSION

Our first patient, who has had arthritis for 21 years, has it now in an advanced stage. He has had repeated infections. Anemia, splenomegaly, and leukopenia have been present for at least five years. It is probable that the

thrombocytopenia has been present for this length of time also, but unfortunately, platelet counts were not done during his first hospitalization in 1941.

In presenting our cases we are not concerned with entering into the discussion as to whether we should label them as cases of so-called Felty's syndrome or, by considering the arthritis merely a coincidence, to classify them with the cases of primary splenic neutropenia which were first described by Doan and Wiseman.<sup>6</sup> Singer and Levy,<sup>11</sup> Talkov, Bauer and Short,<sup>12</sup> and Steinberg<sup>5</sup> have given good discussions of this question. Dameshek<sup>13</sup> believes that "Felty's syndrome is a form of splenic leukopenia due to involvement of the spleen in the chronic infectious or toxic process of the rheumatoid arthritis."

In regard to the mechanism of production of the leukopenia or pancytopenia our cases appear to lend no support to the theory of Doan and Wiseman<sup>6</sup> that the blood cells undergo "sequestration" and phagocytosis by the hyperactive and enlarged spleen; first, because our spleens showed no unusual phagocytosis and secondly, because the anemia which was present in our case 1 was not hemolytic in type. However, it should be mentioned that these investigators state that supravital stains are necessary to demonstrate phagocytosis in the spleen. Such stains were not made in our cases.

Dameshek<sup>14</sup> favors the hypothesis that the enlarged spleen inhibits the blood cells of the bone marrow from either maturation or liberation into the blood stream by means of splenic hormones. We have no evidence in our study for or against this theory. In spite of the disagreement as to its mechanism the proponents of both schools of thought agree as to the reality of the syndrome and the effects of splenectomy.

Our first patient (case 1) differs somewhat from those described by Doan in that the bone marrow was hypoplastic rather than hyperplastic. This absence of hyperplasia gave us much concern regarding the advisability of splenectomy since we feared that the removal of the spleen would be of no avail in the face of what appeared to be a poorly functioning bone marrow. Doan,<sup>6</sup> Muether,<sup>8</sup> and Steinberg<sup>5</sup> all stress the importance of having a hyperplastic bone marrow before subjecting the patient to splenectomy. It is worthy of note that Hanrahan and Miller<sup>3</sup> and also Craven<sup>4</sup> had previously performed splenectomy on their patients without bone marrow biopsies (marrow biopsies being a fairly new procedure at the time). Steinberg,<sup>5</sup> as previously stated, was the first to remove the spleen in so-called Felty's syndrome knowing that the bone marrow was hyperplastic and suggested that there was an inhibition of cell maturation.

In our review of the literature of this subject we could find only four cases which did not show bone marrow hyperplasia. In two of these the marrow was described as normal and in two as hypoplastic. Salzer, Ransohoff and Blatt<sup>22</sup> and Alt<sup>10</sup> reported those with normal marrows which responded to splenectomy with return of the blood pictures to normal. Wil-

liams' <sup>16</sup> case, in which the bone marrow was obtained at autopsy, showed a diminution in granulopoiesis. No splenectomy was done. In the three bone marrow specimens of Moore's patient <sup>7</sup> taken before splenectomy there was relative acellularity which suggested moderate hypoplasia. Here there was an increase in cellularity following operation and all the cellular elements of the peripheral blood returned to normal.

The adrenalin test <sup>15</sup> is considered by Doan and his school as a helpful diagnostic test in deciding on operation. If there is a significant rise in the neutrophils after the hypodermic injection of adrenalin they feel that the spleen is incriminated in the neutropenic syndrome. Lucia, Leonard and Falconer <sup>17</sup> have shown, however, that adrenalin causes an increase in the peripheral granulocytes even in splenectomized patients. They also state that adrenalin does not stimulate the bone marrow, and they conclude that the test is of no diagnostic value. In our first patient there was a small rise in the total leukocyte count with no change in the differential picture. For these reasons we did not feel that the test was of any help to us in deciding whether or not to operate.

At the time when we were considering splenectomy in case 1 we were not aware of Moore's patient who was splenectomized successfully even though there was marrow hypoplasia. However, Dr. H. R. Peters recommended that since the spleen is not essential for life or health <sup>18</sup> we would probably do the patient no harm by removing it. The good result obtained in our patient, as shown by the improvement in his health and vigor and the return to normal of the blood picture, seem to indicate that even with a hypoplastic bone marrow the removal of the spleen is curative.

How does one explain the fact that our first patient and those of Moore and Williams showed a hypoplastic marrow whereas Doan and others stress the importance of a hyperplastic marrow as one of the criteria for the diagnosis of the neutropenic syndrome? It is our feeling that the cases which show a decrease in the cellularity of the bone marrow probably represent the same clinical entity in a different stage of the disease. It is possible that they may previously have had hyperplastic marrow, but owing to the prolonged duration of the disease the bone marrows became exhausted (hypoplastic) as suggested by Darling, Jackson and Parker <sup>19</sup> and Fitzhugh and Krumbhaar <sup>20</sup> in their papers on agranulocytic angina. Some evidence for this possibility is seen in our first case, in which the white cell counts averaged about 3400 and the neutrophils about 70 per cent in 1941 and later dropped to an average of 1500 and 26 per cent, respectively, in 1946 (table 1).

We prefer to classify our patients with the primary splenic neutropenic group rather than with the primary splenic pancytopenic group because, although there were decreases in the red cells and platelets in case 1, these decreases were mild and asymptomatic, and because in case 2 there was a diminution in the granulocytes only.

In regard to the anemia in this blood dyscrasia it should be noted that Doan's cases all showed anemia which was hemolytic in type. In our case with anemia (case 1) no evidence of hemolysis could be demonstrated since the van den Bergh, icteric index and reticulocyte counts were all normal. It is probable that the anemia here was inhibitory in type, as suggested by Abrami<sup>21</sup> who states that splenomegalic anemia may be of two types, hemolytic or inhibitory.

### SUMMARY AND CONCLUSIONS

1. Two cases of primary splenic neutropenia with arthritis (so-called Felty's syndrome) are presented.
2. Both showed clinical improvement following splenectomy with a return to normal of the leukocyte count.
3. The bone marrow in one case was hypoplastic rather than hyperplastic.
4. Splenectomy is of value even in the face of a hypoplastic bone marrow.
5. The mental outlook of the patient is brightened by the knowledge that he is better able to resist infections.

### BIBLIOGRAPHY

1. FELTY, A. R.: Chronic arthritis in the adult associated with splenomegaly and leukopenia, *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 16-20.
2. STILL, G. F.: On a form of chronic joint disease in children, *Méd.-Chir. Trans.*, 1897, lxxx, 47-60.
3. HANRAHAN, E. M., and MILLER, S. R.: Effect of splenectomy in Felty's syndrome, *J. r. Am. Med. Assoc.*, 1932, xcix, 1247-1249.
4. CRAVEN, E. B., JR.: Splenectomy in chronic arthritis associated with splenomegaly and leucopenia (Felty's syndrome), *Jr. Am. Med. Assoc.*, 1932, cii, 823-826.
5. STEINBERG, C. L.: The value of splenectomy in Felty's syndrome, *Ann. Int. Med.*, 1942, xvii, 26-40.
6. WISEMAN, B. K., and DOAN, C. A.: A newly recognized granulopenic syndrome caused by excessive splenic leucolysis and successfully treated by splenectomy, *Jr. Clin. Invest.*, 1939, xviii, 473.
7. MOORE, C. V., and BIERBAUM, O. S.: Chronic neutropenia treated by splenectomy, *New Internat. Clin.*, 1939, iii, part 2, 86-95.
8. MUETHER, R. O., MOORE, L. T., STEWART, I. W., and BROWN, G. O.: Chronic granulocytopenia caused by excessive splenic lysis of granulocytes, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2255-2257.
9. WISEMAN, B. K., and DOAN, C. A.: Primary splenic neutropenia: a newly recognized syndrome closely related to congenital hemolytic icterus and essential thrombocytopenic purpura, *Ann. Int. Med.*, 1942, xvi, 1097-1117.
10. DOAN, C. A.: Primary splenic panhematopenia, *Jr. Lab. and Clin. Med.*, 1945, xxx, 385-388.
11. SINGER, H. A., and LEVY, H. A.: Relationship of Felty's and allied syndromes to sepsis lenta, *Arch. Int. Med.*, 1936, lvii, 576-600.
12. TALKOV, R. H., BAUER, WALTER, and SHORT, C. L.: Rheumatoid arthritis associated with splenomegaly and leucopenia, *New Eng. Jr. Med.*, 1942, ccxxvii, 395-399.
13. DAMESHEK, W.: Leukopenia and agranulocytosis, 1944, *Oxford Loose Leaf Medicine*, New York, ii, part 3, 841-848.

14. DAMESHEK, W.: Editorial, *Blood*, 1946, i, 173-174.
15. DOAN, C. A., and WRIGHT, CLAUDE-STARR: Primary congenital and secondary acquired splenic panhematopenia, *Blood*, 1946, i, 10-26.
16. WILLIAMS, R. H.: Felty's syndrome, report of a case with necropsy findings, *Ann. Int. Med.*, 1936, ix, 1247-1255.
17. LUCIA, S. P., LEONARD, M. E., and FALCONER, E. H.: The effect of the subcutaneous injection of adrenalin on the leukocyte count of splenectomized patients and of patients with certain diseases of the hematopoietic and lymphatic systems, *Am. Jr. Med. Sci.*, 1937, cxciv, 35-42.
18. ROETTIG, L. C., NAUSBAUM, W. B., and CURTIS, G. M.: Traumatic rupture of the spleen, *Am. Jr. Surg.*, 1943, lix, 292-319.
19. DARLING, ROBERT C., PARKER, FREDERIC, JR., and JACKSON, HENRY: The pathological changes in the bone marrow in agranulocytosis, *Am. Jr. Path.*, 1936, xii, 1-10.
20. FITZ-HUGH, THOMAS, JR., and KRUMBHAAR, E. B.: Myeloid cell hyperplasia of the bone marrow in agranulocytic angina, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 104-110.
21. ABRAMI, P., D'ALLAINES, F., and DUGAS, J.: Du mécanisme de l'anémie au cours des anémies spléniques de l'adulte. Splénomégaties hémolytiques et splénomégaties myélo-péniques, *La Sang*, 1944, xvi, 213-218.
22. SALZER, MOSES, RANSOHOFF, J. LOUIS, and BLATT, HERMAN: Primary splenic neutropenia, with report of a case, *Ann. Int. Med.*, 1945, xxii, 271-273.

# CHRONIC HEADACHE DUE TO MASKED HYPOTHYROIDISM \*

By NATHAN M. FENICHEL, M.D., F.A.C.P., *Brooklyn, New York*

ONE of the most baffling conditions a physician is called upon to treat is a chronic distressing headache in which a thorough physical examination, including a survey of the eyes, nose, and central nervous system, is essentially negative. Many of these patients are noticeably nervous and apprehensive, yet assurance and sedation do not produce amelioration.

In the past few years I have collected a group of 20 patients with distressing headaches in which the basal metabolism was found to be below normal (table 1). With the administration of thyroid extract these patients obtained gratifying relief. In many the headaches had previously been considered psychogenic in origin, since no other demonstrable etiology could be discovered upon examination.

TABLE I

Case	Patient	Age	Weight	Headache	Sensitivity to Cold	Fatigue	Initial B.M.R.	Resting Pulse	Improvement with Thyroid
1	S. F. ♀	26	N	Severe frontal	+	+	-17	60	Marked
2	S. Z. ♀	35	U	Dull diffuse	0	+	-25	76	Marked
3	M. R. ♀	43	N	Frontal-occipital	+	+	-21	66	Marked
4	M. S. ♀	47	N	Dull vertical	0	+	-13	58	Marked
5	D. S. ♀	36	N	Throbbing occipital	+	+	-19	56	Moderate
6	C. S. ♀	38	N	Dull vertical	+	+	-26	70	Marked
7	M. S. ♀	46	N	Dull diffuse	0	+	-18	64	Marked
8	S. W. ♀	26	N	Dull diffuse	+	+	-22	56	Marked
9	E. H. ♀	32	N	Diffuse	+	+	-24	66	Marked
10	F. F. ♀	55	N	Dull frontal	+	+	-24	56	Moderate
11	C. M. ♀	39	O	Dull diffuse	0	0	-18	60	Marked
12	R. S. ♀	44	N	Severe diffuse	0	+	-17	60	Slight
13	M. S. ♀	39	O	Dull diffuse	0	0	-16	70	Marked
14	Y. T. ♀	37	U	Dull diffuse	0	+	-20	70	Moderate
15	B. Z. ♀	37	U	Dull diffuse	0	+	-12	68	Moderate
16	D. L. ♀	41	O	Dull diffuse	0	+	-21	66	Slight
17	M. D. ♀	32	N	Left occipital	0	+	-15	58	Slight
18	J. S. ♂	40	U	Vertical	0	+	-16	60	Marked
19	M. K. ♂	38	O	Diffuse	0	0	-13	56	Marked
20	S. L. ♂	50	O	Dull diffuse	0	+	-14	58	Moderate

N denotes normal weight, U underweight, and O overweight.

The headache in these patients was usually constant throughout most of the day and often persisted for weeks at a time. It was accentuated by undue physical strain or excitement and relieved by rest. The headache was char-

\* Received for publication February 7, 1947.

From the Medical Services of the Brooklyn Jewish Hospital and the Kings County Hospital.

acteristically bilateral in its distribution and sometimes localized to either the occipital, the vertical, or the frontal area. In other patients its distribution was vague. The cephalalgia varied in intensity from a dull annoying distress to a severe throbbing ache. It differed quite distinctly from typical migraine in that the headache was not periodic, unilateral, nor accompanied by nausea and vomiting. It is interesting to note that two of the patients (cases 13 and 15) suffered in addition from attacks of typical migraine, but they did not obtain any relief from the seizures of hemicrania while under thyroid therapy.

Aside from some vague clinical suggestions, there were no pronounced stigmata obtained in history or physical examination to indicate hypothyroidism in this group. Only one of the entire series exhibited moderate myxedema with obvious clinical evidence of hypothyroidism. The remaining patients did not appear sluggish and, on the contrary, many were quite apprehensive and alert. Seventeen of the 20 remarked that they became easily exhausted especially towards evening. Seven of the 20 complained of unusual sensitivity to cold upon exposure. Some did remark on the lack of appreciable perspiration in hot weather. None showed any unusual dryness or puffiness of the skin. Some patients commented on some depletion of hair from the scalp, but in none was any thinning of the eyebrows detected. There was no unusual distribution of fat, and only five of the group were slightly or moderately obese, 11 being normal in weight and the remaining four underweight.

The series was composed predominantly of females, 17 of the 20, and their ages ranged from 26 to 55 years. Their basal metabolic rates varied between — 12 per cent to — 26 per cent. The one patient exhibiting clinical myxedema registered the lowest rate. Blood cholesterol values were obtained in only two of the patients and were normal.

Desiccated thyroid extract in daily doses of 1 to 3 grains brought about considerable amelioration of the headaches in 17 of these patients, usually after a latent period of 10 to 14 days, and the basal metabolic rate gradually rose to normal. Many felt as though a weight had been removed from their heads and they expressed surprise at their greater energy. It was found best to start therapy with a smaller dose, 1 grain daily, since these patients were found to be sensitive to thyroid and larger initial doses occasionally produced palpitation and irritability. Three patients obtained only slight relief from the headaches, but of these, two also suffered from hypertension (cases 12 and 16). The remaining 18 patients all had a blood pressure usually within the range of low normal. A moderate secondary anemia, observed in only two patients, did not respond to iron therapy alone, but did improve on combined iron and thyroid medication.

This group of patients is part of a larger series of 44 patients with mild hypothyroidism and low basal metabolic rates, who were all observed during the same period. The remaining patients did not experience any headaches



but did complain of asthenia, lethargy, intolerance to cold, or excessive loss of hair from the scalp, and they also manifested improvement with thyroid medication.

As defined by Werner,<sup>1</sup> hypothyroidism is a condition in which the thyroid gland fails to supply sufficient internal secretion to the tissues of the body to maintain chemical activity at a normal level. It seems that the headaches of which these patients complained resulted from the additional stress and strain under which they were laboring because of a deficiency in circulating thyroid hormone. Their response to thyroid therapy tends to confirm this view, especially since previous treatment with aspirin or sedatives was ineffective.

Means<sup>2</sup> has noted that some perfectly healthy individuals may record a low metabolic rate and terms this hypometabolism without any clinical significance. This is illustrated by several other patients who exhibited a low basal metabolic rate as an isolated finding and who did not require thyroid, nor were they helped if given the drug. These patients felt entirely well or presented symptoms unrelated to hypothyroidism. However, the patients presented in this report are undoubtedly true cases of hypothyroidism which are milder than those seen with the features of myxedema. As a matter of fact, most of the patients that I have seen with pronounced clinical manifestations of myxedema are too dull and apathetic to complain of headache.

That chronic persistent headache is common in mild hypothyroidism has been recorded previously by other observers. Higgins<sup>3</sup> in 1925 noted that some of his cases of mild hypothyroidism complained of headache and fatigue. Seward<sup>4</sup> in 1935 observed 53 patients with the mild type of hypothyroidism in which 18 suffered from headaches either at the vertex or in the suboccipital area. Schultz<sup>5</sup> in 1936 reported a group which she termed non-myxedematous hypothyroidism and emphasized neurasthenia and generalized headaches as conspicuous clinical features. Harstock<sup>6</sup> in 1939 presented a large group of patients which he classified as incipient hypothyroidism. He remarked that 75 per cent of these patients would be overlooked, if one expected to find some of the typical features of myxedema for the diagnosis. Many of his patients complained of chronic headache which he<sup>6</sup> attributed to their general fatigue and hypotension. Werner<sup>1</sup> in 1942 also noted that some of his patients with mild hypothyroidism suffered from aching in the occipitocervical region with radiation to the shoulders and interscapular area.

To be sure, hypothyroidism is not a frequent cause of headache among the various patients with this complaint seen in practice. Nevertheless this type is remarkable because of its chronicity, its annoying disability, and its favorable response to thyroid therapy.

The following four illustrative cases are briefly presented.

## CASE REPORTS

*Case 1.* Mrs. S. F., aged 26, was first seen in March 1937 complaining of almost continuous bilateral frontal headaches increasing in severity toward evening. She felt very irritable and readily became exhausted, finding it difficult to do her housework. She experienced chilliness on exposure to cold and preferred warm weather. Physical examination revealed a tall alert young woman of normal weight, with a blood pressure of 120 mm. Hg systolic and 80 mm. diastolic, and a pulse rate of 60. Otherwise examination was essentially normal, the blood Wassermann reaction was negative, and the urine normal. Sedatives and aspirin were prescribed without any relief. A change of glasses recommended by an ophthalmologist, and several nasal drainages for suspected sinusitis did not alleviate the headaches. In July 1937, a basal metabolism test recorded a rate of  $-17$  per cent, and desiccated thyroid 2 grains daily was prescribed. Within two weeks the headaches had entirely disappeared and the patient felt as though rejuvenated. She continued to take thyroid, averaging 1 to 2 grains daily, almost continuously for nine years, during which time she bore two children. When she stopped taking the drug for over a month, the headaches and tiredness returned. In January 1944 her basal metabolic rate was  $-12$  per cent while on 1 grain of thyroid daily. At no time did she demonstrate any clinical signs suggestive of myxedema.

*Case 2.* Miss S. Z., aged 35, was seen in December 1944 with complaints of extreme weakness, nervousness, chronic fatigue, and a constant ache vaguely distributed over the entire head. The headache would often become much more severe at night and would then localize at either temple. Examination disclosed an active woman with bright prominent eyes of the familial type. She was considerably underweight, her blood pressure was 138 mm. Hg systolic and 90 mm. diastolic, and her pulse rate was 76. Despite a high caloric diet and sedatives, her headaches continued, and she was unable to gain weight. In April 1945, a basal metabolism test revealed a surprisingly low rate of  $-25$  per cent, while her resting pulse rate was 74. Blood cholesterol was 210 mg. per cent. On 1 grain of thyroid daily there was a slight improvement and when the dose was doubled, she became completely relieved of her headaches, gained some weight, and felt much more energetic. In May 1945, she stopped the thyroid medication for six weeks and experienced a return of headaches and lethargy. In March 1946 her basal metabolic rate was  $-10$  per cent while on 10 grains of thyroid per week.

*Case 8.* Mrs. S. W., aged 26, was seen in June 1943 because of weakness, dizziness, and frequent headaches. The headaches recurred regularly every afternoon, were diffuse in distribution, and were associated with subjective dizziness. Aside from some evident pallor, nothing remarkable was found upon examination. Her blood pressure was 110 mm. Hg systolic and 80 mm. diastolic, and her weight was normal. A blood study revealed a hemoglobin 64 per cent Sahli, red blood cells 3,100,000, and white blood cells 6,200 of which 45 per cent were neutrophils, 43 per cent lymphocytes, 7 per cent monocytes, and 5 per cent eosinophiles. Blood cholesterol was 240 mg. per cent. A stool examination was negative for parasites. Despite large doses of iron, the hemoglobin remained stationary and the symptoms persisted. She also remarked that she felt quite sensitive to cold. In October 1943 a basal metabolic rate of  $-22$  per cent was recorded, while the resting pulse rate was 56. Desiccated thyroid 1 grain daily was prescribed and the iron medication continued with some improvement. In December the daily dose of thyroid was increased to 2 grains, and she experienced a complete remission in that she no longer suffered headaches nor dizziness and had gained some weight and strength. Her hemoglobin rose to 80 per cent. In October 1946 her basal metabolic rate was  $-9$  per cent, while on 2 grains of thyroid daily.

*Case 18.* Mr. J. S., aged 40, visited me in March 1946 with diversified complaints of asthenia, dizziness, dull precordial distress, and generalized muscular aches. A diagnosis of neurocirculatory asthenia was made, and he improved with sedatives and psychotherapy. In June 1946 his symptoms recurred together with a continuous distressing headache centered particularly on the top of his head. Examination revealed nothing of note, his weight was slightly below normal, and his blood pressure was 108 mm. Hg systolic and 70 mm. diastolic. A basal metabolic rate of  $-16$  per cent was obtained, and desiccated thyroid 1 grain daily was prescribed. After nine days, the headaches disappeared and there was a considerable improvement in his neurasthenic symptoms. In September, while on thyroid therapy, he felt much stronger than he had felt for years and experienced no headaches.

### SUMMARY

A bilateral headache, remaining for weeks, may be due to mild hypothyroidism which is not readily recognized by physical examination.

Suggestive features of such masked hypothyroidism are asthenia, sensitivity to cold, slow resting pulse rate, and a moderate hypotension.

The basal metabolic rate should be determined in any patient complaining of persistent headaches, in whom no cause is discernible upon routine history and physical examination.

This type of headache is remarkable for its favorable response to thyroid medication.

### BIBLIOGRAPHY

1. WERNER, A. A.: *Endocrinology, clinical application and treatment*, 1942, Lea and Febiger, Philadelphia, p. 570.
2. MEANS, J. H.: *Thyroid and its diseases*, 1937, J. B. Lippincott Co., Philadelphia, p. 526.
3. HIGGINS, W. H.: Incipient hypothyroidism, *Jr. Am. Med. Assoc.*, 1925, lxxxv, 1015.
4. SEWARD, B. P.: A clinical study of mild hypothyroidism, *Ann. Int. Med.*, 1935, ix, 178.
5. SCHULTZ, H. E.: Non-myxedematous hypothyroidism, *Jr. Michigan State Med. Soc.*, 1936, xxxv, 97.
6. HARSTOCK, C. L.: Clinical aspects of hypothyroidism, *Cleveland Clin. Quart.*, 1939, vi, 53.

## RENAL GLYCOSURIA: A REVIEW OF THE LITERATURE AND REPORT OF FOUR CASES \*

By JOHN H. BLAND,† Capt., M.C., A.U.S., *Burlington, Vermont*

IN the evaluation of the meliturias, renal glycosuria is usually considered a rare clinical entity. However, some recent studies refute this impression or at least bring its validity into question. The condition is benign and carries a good prognosis. The likelihood of its being accorded serious import or even being treated as diabetes mellitus, gives renal glycosuria a prominent place in the diagnostic consideration of the medical work-up of any case of melituria. The reports of Blotner and Hyde<sup>1</sup> and the Peels<sup>2</sup> regard renal glycosuria as a relatively common finding, the former reporting one person in 11 with melituria as having the disorder. The rigid diagnostic criteria of Marble,<sup>3</sup> however, were apparently not closely followed. Joslin<sup>3</sup> and his associates in a review of 18,000 cases of melituria report 53 cases of renal glycosuria per se and nine cases of renal glycosuria of pregnancy. Wilder<sup>4</sup> has reported 82 cases from the Mayo Clinic and Fowler<sup>5</sup> noted seven cases of renal glycosuria in 4,000 cases of melituria at the Montreal General Hospital. The highest incidence was seen in the report of the Peels<sup>2</sup> with 30 cases of renal glycosuria in only 115 recruits manifesting melituria. It is interesting to note that the two reports with the highest incidence of the condition occurred in series conducted on recruits who were predominantly of the younger age group.

Marble,<sup>3</sup> who is of the opinion that renal glycosuria is a rare condition, has set the following criteria for the diagnosis. In view of the importance of absolute diagnosis, these standards should be fulfilled prior to making the diagnosis.

1. Fasting blood sugar within normal limits and a normal glucose tolerance curve.

2. Glucose should be present in appreciable quantity in all urine specimens, whether voided in the fasting state or post-prandially. The quantity of sugar in the urine should be for the most part independent of the diet.

3. Carbohydrate utilization should be normal as evidenced by the respiratory quotient and serum inorganic phosphate after glucose ingestion.

4. Fat metabolism should be normal, ketosis being more likely to develop when the patient fasts than when he overeats.

5. Moderate doses of insulin should have little or no effect on the glycosuria.

The Station Hospital, Camp Hood, Texas, admitted 5,740 patients from May 31, 1946 to February 28, 1947, four of whom had renal glycosuria.

\* Received for publication August 28, 1947.

† Now, Fellow in Department of Experimental Medicine, College of Medicine, University of Vermont, Burlington, Vt.

The diagnosis in these patients conformed to the requisites as presented by Marble. The hospital receives military personnel and their dependents and veterans of all age groups.

## CASE REPORTS

*Case 1.* A 30 year old white male was admitted to the hospital June 19, 1946, with complaint of dysuria, frequency and nocturia of four months' duration. His past medical history disclosed that he had had an episode of hematuria in the spring of 1943. He was in England at the time and was hospitalized in an Army General Hospital for three months. He was cystoscoped and informed that he had "irritation of the bladder." He was hospitalized on two more occasions, once overseas and once in a zone of the interior general hospital. The patient had six cystoscopic examinations in all. He was asymptomatic from November 1945 to March 1946. His family history revealed no pertinent familial or environmental factors. No members of his family have been known to have diabetes mellitus. He had had gonorrheal urethritis in 1941 and in 1946, being treated with sulfadiazine and penicillin respectively.

The patient was 64 inches in height and weighed 132 pounds. The blood pressure was 126 mm. Hg systolic and 80 mm. diastolic. The physical examination presented no gross abnormalities other than prostatic tenderness, though the gland was not enlarged and was of normal consistency.

The blood count revealed 4,170,000 erythrocytes; 14.5 gm. hemoglobin; and 7,250 leukocytes with a normal distribution. The sedimentation rate (Wintrobe) was 1 mm. per hour. The urinalysis disclosed a 1 plus sugar test using Benedict's qualitative solution, the color being green after 5 minutes' boiling. There were 8 to 10 leukocytes per high power field (centrifuged). The Kahn reaction was negative. A fasting blood sugar determination (Folin-Wu) revealed a finding of 92.6 mg. per cent and the fasting urine specimen showed a 2 plus reduction. Further blood chemical studies of total protein and albumin-globulin ratio, non-protein nitrogen, plasma cholesterol and serum phosphorus were within normal limits. An intravenous pyelogram and chest roentgen-ray presented no abnormalities. The urinary sugar was identified as glucose using as criteria the positive reduction test and the formation of typical glucosazone crystals with phenylhydrazine.

A glucose tolerance test was done using venous blood. The Folin-Wu method was used; simultaneous phosphorus determinations were made; 1.75 grams of glucose per kilogram of body weight were given orally after 12 hours fasting. The figures below demonstrate the result of this test, disclosing a normal tolerance to glucose. The fall in phosphorus values proves adequate absorption of the glucose.

Glucose Tolerance Test			
	Blood Sugar	Phosphorus	Urine Sugar
Fasting	86.4 mg. %	5.8 mg. %	Trace
$\frac{1}{2}$ hr.	141.6 mg. %	3.6 mg. %	4 plus
1 hr.	136.4 mg. %	2.6 mg. %	3 plus
2 hr.	96.0 mg. %	3.0 mg. %	3 plus
3 hr.	78.4 mg. %	3.2 mg. %	1 plus

Urine specimens were collected every hour on the hour for 24 hours and each specimen manifested quantities of sugar varying from a trace to 2 plus. The quantitative determination of the 24 hour specimen for sugar was 0.64 gram per cent. The patient in a fasting state received 15 units of crystalline insulin subcutaneously which

did not affect the glycosuria. He was never found to be without glycosuria. A diet containing 400 grams of carbohydrate, 130 grams protein and 100 grams of fat was given the patient for three days. His subsequent urine specimens and those of the third day of his diet continued to show persistent glycosuria with no appreciable change in the amount of sugar. There was likewise no change in urinary sugar on a diet of carbohydrate 100 gm., protein 60 gm. and fat 60 gm.

This patient had been treated on two occasions for diabetes mellitus using both insulin and dietotherapy. There were multiple cystoscopic examinations made which may or may not have been necessary. At any rate, this patient's melituria had not received adequate study to establish its type and warrant a conclusion regarding disposition of the man. He came to the hospital for Certificate of Disability Discharge on the basis of diabetes mellitus and has since returned to duty and has been asymptomatic for six months.

*Case 2.* A 21 year old white male was admitted to the hospital January 8, 1947, for tonsillectomy. He was a tall asthenic individual with a history of severe recurrent tonsillitis of 18 months' duration and complaints of easy fatigability and a mild progressive asthenia of about six months' duration. The finding of a 1 plus melituria and a 1 plus albuminuria had never occurred before to the patient's knowledge. His last urinalysis was May 7, 1944. He had done considerable duty in the South Pacific. He stated that there was "lots of kidney trouble" in his family. He has one brother who has diabetes mellitus.

The tonsils were embedded and cryptic. There was a cardiac arrhythmia exaggerated by exercise and rapid respiration which was interpreted as multiple auricular premature contractions with an associated sinus arrhythmia.

The urine continued to manifest a 1 plus albuminuria and varying degrees of melituria. The blood count was normal; blood chemistry determinations were normal for serum cholesterol, blood urea, phosphorus and sugar; Kahn test was negative. Three basal metabolic rates were within normal limits. A urea clearance test of renal function was normal. The chest roentgen-ray disclosed no abnormalities. The patient's electrocardiogram demonstrated multifocal auricular and ventricular premature contractions with occasional atrio-ventricular dissociation. Sinus arrhythmia was present in marked degree. The tracing was otherwise normal. His glucose tolerance test, using the method above described, demonstrated a normal tolerance for glucose. Both arterial and venous blood sugars were done to note the arteriovenous difference and determine whether or not adequate utilization was occurring in the tissues. Serum phosphorus determinations were made simultaneously to study glucose absorption. (The capillary micro-method of Folin-Wu was used to determine the arterial blood sugars.)

Glucose Tolerance Test

	Blood Sugar		Phosphorus	Urine Sugar
	Arterial	Venous		
Fasting	91.7 mg. %	82.6 mg. %	5.5 mg. %	1 plus
½ hr.	208.3 mg. %	163.9 mg. %	3.8 mg. %	2 plus
1 hr.	256.4 mg. %	178.6 mg. %	3.8 mg. %	4 plus
2 hr.	210.5 mg. %	151.5 mg. %	3.6 mg. %	4 plus
3 hr.	121.2 mg. %	71.7 mg. %	4.0 mg. %	4 plus

The urinary sugar was identified as glucose. Hourly urine specimens collected around the clock all contained glucose in varying significant quantities and the quantitative determination on the 24 hour specimen disclosed 0.6 gm. per cent glucose. There was no change in the glycosuria with either a high or low carbohydrate diet. The administration of insulin did not alter the glycosuria. All specimens of urine manifested a 1 plus to 2 plus albuminuria with from 10 to 20 leukocytes in a centrifuged specimen. No erythrocytes were seen.

The study of this patient suggests that his renal glycosuria had its onset some time between 1944 and 1947. The history of severe, recurrent tonsillitis also suggests a streptococcal origin of widespread vascular disease with, perhaps, an allergic-hyperergic response on the part of the heart and the kidneys. This idea is based on the conception of the rheumatic syndrome as advanced by Coburn. It is conceivable that enough vascular damage could have occurred to the blood supply of the renal tubules to alter the reabsorption gradient of glucose by disrupting the enzyme system concerned with its reabsorption from the tubules. The phosphorylation mechanism of glucose reabsorption from the tubules has been postulated.

*Case 3.* A 28 year old white male was admitted to the hospital on February 18, 1947, for a nasal sub-mucous resection and rhinoplasty. His history was that of severe frontal and occipital headaches and chronic cough productive of thick, gray, nummular sputum. He stated that he had had a "constant cold" for six years. The patient had had scarlet fever as a child and a tonsillectomy at the age of 13 years. The family history was negative. He smoked about one and a half packages of cigarettes a day. There were offered complaints of urinary frequency and nocturia, three or four times nightly; ease of fatigue; night sweats; "nervousness," apprehension and anorexia. His physical examination revealed a markedly deviated nasal septum and a thick turgescient nasal mucosa. His blood pressure was 122/76.

The Mantoux test was 1 plus. His blood chemistry studies, including blood urea, fasting blood sugar and cholesterol, were normal. The blood count was normal except for a leukocytosis of 13,000 cells with 82 per cent predominance of polymorphonuclear cells. Paranasal sinus and chest roentgen-rays were normal as was the electrocardiogram. The urinalysis was normal except for a 2 plus melituria. The sugar was identified as glucose. A blood urea clearance test was within normal limits. The glucose tolerance test using arterial and venous sugar determinations plus simultaneous phosphorus studies is shown below.

Glucose Tolerance Test				
	Blood Sugar		Phosphorus	Urine Sugar
	Arterial	Venous		
Fasting	92.0 mg. %	72.2 mg. %	5.7 mg. %	Neg.
$\frac{1}{2}$ hr.	177.0 mg. %	127.4 mg. %	3.4 mg. %	2 plus
1 hr.	114.3 mg. %	86.6 mg. %	2.8 mg. %	3 plus
2 hr.	97.3 mg. %	81.6 mg. %	2.4 mg. %	1 plus
3 hr.	57.2 mg. %	46.0 mg. %	3.6 mg. %	1 plus

This test demonstrates normal glucose absorption and tissue utilization. This patient, in contradistinction to the others, had negative urine sugar tests from about midnight until after breakfast the next morning. All other urine specimens obtained

hourly contained quantities of glucose varying from a trace to 3 plus. The quantitative glucose determination on the 24 hour specimen was 0.64 gm. per cent glucose. The urinary glucose was not affected by a high or low carbohydrate diet as described in case 1. Crystalline insulin in a dosage of 15 units subcutaneously was given in the fasting state and the glycosuria remained unchanged as determined in hourly urine specimens collected for six hours.

This case does not completely satisfy the rigid criteria of Marble in that the patient was aglycosuric from midnight until 7 a.m. However, all other types of melituria were excluded and it was felt that the diagnosis could be tentatively made. It may be noted that low values for sugar were obtained in the last specimens of the glucose tolerance test. There were no hypoglycemic symptoms noted and it was thought that these low values may be attributed to the method of determination used. It is now recognized that the Folin-Wu method gives results which are too low for low values and too high for high values. Cantarow and Trumper<sup>6</sup> note that "the Benedict's 1928 and 1931 reagents which may be used with the Folin-Wu tungstic-acid filtrate, are relatively unaffected by glutathione and other saccharoids. The use of the Benedict's reagent lessens the possibility of errors of interpretation due to this inaccuracy of method."

*Case 4.* A 26 year old white soldier was admitted to the hospital February 20, 1947, for hemorrhoidectomy. This patient was first told that he had sugar in his urine in 1937 and was treated for diabetes mellitus for several months by dietotherapy but received no insulin. He had stopped treatment of his own accord. The patient has one brother who has diabetes and is treated with both diet and insulin. One sister has melituria but has never been treated. A paternal uncle has diabetes mellitus requiring both insulin and diet for its control. The patient's mother has hypertensive cardiovascular disease. The remainder of the history and systemic review were negative. The physical examination was negative except for pharyngeal adenopathy and large external hemorrhoids.

The blood count was normal and the urinalysis disclosed a 3 plus melituria. Blood chemical tests, including the blood urea, fasting blood sugar and cholesterol determinations, were normal. A blood urea clearance test of renal function was within normal limits. The chest roentgen-ray and electrocardiogram showed no abnormalities. The glucose tolerance test is shown below. This test demonstrates normal glucose absorption and tissue utilization. It also suggests an increased tolerance to glucose which in turn suggests either a decreased rate of hepatic glycogenolysis or increased tissue glycogenesis and glycolysis.

Glucose Tolerance Test

	Blood Sugar		Phosphorus	Urine Sugar
	Arterial	Venous		
Fasting	84.4 mg. %	81.0 mg. %	3.88 mg. %	3 plus
$\frac{1}{2}$ hr.	117.5 mg. %	101.5 mg. %	3.84 mg. %	4 plus
1 hr.	85.8 mg. %	71.7 mg. %	3.07 mg. %	4 plus
2 hr.	86.9 mg. %	62.3 mg. %	3.06 mg. %	3 plus
3 hr.	70.2 mg. %	53.3 mg. %	3.20 mg. %	3 plus



The urinary sugar was identified as glucose. Hourly sugar determinations on the urine were made for 24 hours and each specimen contained 2 plus to 4 plus sugar. Only two of these specimens were 2 plus, 12 were 4 plus and 10 were 3 plus. The quantitative determination for sugar on the 24 hour specimen was 0.77 gram per cent of glucose. Crystalline insulin was given subcutaneously as described above and the glycosuria was unaffected. There was noted no change in the glycosuria when the patient was placed on both high and low carbohydrate diet as described in the first case.

The family history in this case was interesting in that there are apparently two true diabetics in the family and one person with melituria of undetermined type. The familial incidence of renal glycosuria has been pointed out by Brown and Poleshuck.<sup>7</sup> It is not known whether members of the patient's family represent cases of true diabetes or renal glycosuria. Blotner and Hyde report a family history of diabetes in 32 per cent of 22 patients with renal glycosuria.

This patient also has been treated for diabetes mellitus though only for a short time. Thoroughgoing study of such individuals is certainly indicated in that they frequently offer difficult problems and are apparently frequently mistaken for true diabetes. According to present knowledge renal glycosuria is an innocuous disorder and hence correct diagnosis is of considerable importance to the patient.

#### COMMENT

Renal glycosuria is a condition which is considered by most authorities to be rare. However, Blotner and Hyde and the Peels report a rather high incidence by comparison with other authors. At any rate it seems likely that many people with melituria of some type are being needlessly treated for diabetes mellitus. There is little doubt that real damage may be done by such therapy. If such a patient is losing sugar steadily in his urine, it would seem only sensible that a liberal carbohydrate diet is indicated. Certainly insulin administration can be of no value in the treatment of renal glycosuria and may well do considerable harm. These patients frequently complain of ease of fatigue and malaise which symptoms may well have their origin in a low carbohydrate intake. Marble recommends prolonged observation in these patients because of the strong family history of diabetes. Renal glycosuria and diabetes mellitus are two separate entities and the consensus is that the former does not progress to diabetes. True idiopathic renal glycosuria is regarded as a permanent condition which is in most instances asymptomatic or only mildly so.

Renal glycosuria is characterized by a low renal threshold for sugar. It is well established that the urinary sugar is present because of incomplete reabsorption of sugar by the proximal convoluted tubules of the kidneys. The reason for this abnormality is not well understood. All of the cases reported here have low renal thresholds as proved by the presence of glycosuria with a normal or subnormal level of blood sugar. It has been postu-

lated that a deficiency of tissue phosphatase may be the abnormality producing consequent interference with the phosphorylation mechanism in the renal tubules on which sugar reabsorption depends. Another possible etiology is that suggested by Thomas and Southward who conjecture that the renal threshold is under hormone control. Comparison is made with diabetes insipidus in which the hormone of the posterior pituitary exerts its well known effect on the renal tubules. The renal glycosuria of pregnancy fits this conception in that there exists in pregnancy a hormonal imbalance. The second case in this group apparently developed his renal glycosuria following a series of streptococcal infections. The thought that this may be more than coincidental is offered. The widespread vascular lesions apparently produced by repeated hemolytic streptococcal infections may well produce changes in the blood supply to the renal tubules which in turn could alter the tubular physiological function. There is no experimental evidence that has come to the author's attention to support this conjecture. Brush<sup>9</sup> reports renal glycosuria as a "complication of advancing age, and is found particularly in individuals who have had some type of obstructive uropathy." He states that "experimental work has proved that functional changes in the kidneys may preëxist macroscopic and microscopic evidence of altered structure." He postulates that these functional changes may be due to extra-renal influences such as degenerative disease of the cardiovascular system or organs or to intra-renal disturbances.

The treatment of renal glycosuria is simple. A liberal and varied diet should be given with perhaps some emphasis on carbohydrate intake. The patient should be advised that his condition is benign and reassured that his prognosis is good. Certainly insulin is not indicated. If the diagnosis of diabetes mellitus is suspected but not proved, there is no indication for haste in instituting therapy. Naunyn's principle of determining the carbohydrate balance by giving a measured diet and estimating the loss of glucose in the urine daily seems worthy of mention. Insulin used in a patient with depleted hepatic glycogen stores may produce acetonemia and acetonuria. Somogyi<sup>10</sup> has shown that a low carbohydrate intake and ill-advised use of insulin may produce increased hepatic glycogenolysis with each episode of hypoglycemia, thus leading to increased hepatic fat and protein metabolism. There occurs consequent increase in ketone production. A clinical ketonuria may thus be induced in the absence of glycosuria. Insulin in such an instance is clearly contraindicated.

#### SUMMARY

1. The literature of renal glycosuria is reviewed and four cases of the disorder are reported. The diagnostic criteria of Marble are used in making the diagnosis.

2. Emphasis is placed on the importance of thoroughgoing study of any case of melituria and the difficulties encountered in discriminating renal glycosuria from diabetes are considered.

3. The study included determinations of both arterial and venous blood sugars in the glucose tolerance tests in order to prove adequate removal of glucose by the tissues from the arterial blood. Serum phosphorus determinations were simultaneously made to study the absorption of the glucose and the phosphorylation mechanism.

4. All cases occurred in military personnel which adds to the importance of accurate diagnosis and consequent disposition of these patients from army hospitals.

5. The dangers of treating renal glycosuria as diabetes are reviewed.

#### BIBLIOGRAPHY

1. BLOTNER, HARRY, and HYDE, R. W.: Renal glycosuria in selectees and volunteers, Jr. Am. Med. Assoc., 1943, cxxi, 432-435.
2. PEEL, A. A. F., and PEEL, M. W.: Glycosuria in recruits, Glasgow Med. Jr., 1941, cxxxv, 141.
3. JOSLIN, E. P., ROOT, H. F., WHITE, PRISCILLA, and MARBLE, ALEXANDER: The treatment of diabetes mellitus, ed. 7, 1940, Philadelphia, p. 714.
4. WILDER, R. M.: Clinical diabetes mellitus and hyperinsulinism, 1940, W. B. Saunders Company, Philadelphia and London, p. 28.
5. FOWLER, A. F.: Renal glycosuria, Ann. Int. Med., 1933, vii, 518.
6. CANTAROW, ABRAHAM, and TRUMPER, MAX: Clinical biochemistry, ed. 2, 1940, W. B. Saunders Company, Philadelphia and London, Chapter 1.
7. BROWN, M. S., JR., and POLESHUCK, RUBIN: Familial renal glycosuria, Jr. Lab. and Clin. Med., 1935, xx, 605.
8. THOMAS, H. M., JR., and SOUTHWORTH, H.: The renal threshold for glucose (clinical observations on a case of non-diabetic (renal) glycosuria), Ann. Int. Med., 1939, xii, 1560.
9. BRUSH, F. H.: Jr. Urol., 1945, liii, 362-364.
10. SOMOGYI, M.: Effects of insulin upon the production of ketone bodies, Jr. Biol. Chem., 1941, cxli, 219.
11. MARBLE, ALEXANDER: The diagnosis of the less common meliturias, Med. Clin. N. Am., 1947, xxxi, 313-326.
12. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practice, ed. 3, 1943, The Williams and Wilkins Company, Baltimore, Md.
13. DREY, N. W.: Non-diabetic glycosuria with comments concerning the significance of insulin-induced ketonuria: a case report, Jr. Clin. Endocrinol., 1944, iv, 447-449.
14. DUNCAN, G. G.: Diseases of metabolism, 1942, W. B. Saunders Company, Philadelphia, Chapters II, XIII, XIV, XV and XVI.
15. SPELLBURG, M. A., and LEFF, W. A.: Incidence of diabetes and glycosuria in inductees, Jr. Am. Med. Assoc., 1945, cxxx, 246-250.
16. WOLMAN, I. J.: Melituria in healthy American men with special reference to transitory glycosuria, Am. Jr. Med. Sci., 1946, ccxii, 159-165.

# DIFFERENTIAL DIAGNOSIS BETWEEN MEDICAL AND SURGICAL JAUNDICE BY LABORATORY TESTS \*

By HANS POPPER, M.D., Ph.D., F.A.C.P., and FREDERICK STEIGMANN, M.D., M.S., F.A.C.P., *Chicago, Illinois*

DESPITE the great strides of laboratory medicine in the past two decades and the subsequent elaboration of many liver function tests, the jaundiced patient still presents today a challenging diagnostic problem. There is little difficulty in recognizing the hemolytic variety of jaundice (retention type) primarily by the absence of bile from the urine, the low or absent direct serum bilirubin and evidence of hemolysis. However, to differentiate the two types of regurgitation jaundice, the medical (due to acute or chronic hepatitis or to cirrhosis) from the surgical (due to stones, tumors or strictures), is often difficult. Even the experienced clinician concedes a relatively high number of diagnostic failures as evidenced by superfluous as well as by delayed operations. The hope of improving this unsatisfactory situation by developing new liver function tests has to date only partly materialized.

The performance of a number of different liver function tests was therefore recommended—a “composite” study of liver function.<sup>1</sup> This created a problem of how to dovetail the results of the different tests into a unified diagnostic approach. Among several presented attempts,<sup>2, 3, 4, 5, 6, 7, 8</sup> the profile derived from graphic recording of the results of liver function tests in a given case as described by Watson and Hoffbauer<sup>1</sup> appeared promising.<sup>9</sup> Nevertheless, to date, profiles characteristic of individual conditions are not as yet available. Moreover, profound knowledge of the physiologic basis is needed for the interpretation of the “composite” study of liver function.

Another approach to be presented below is to trace the thought processes which lead to a diagnosis in a jaundiced patient, and to analyze the rôle which the results of liver function tests play in them. To simplify this otherwise unwieldy problem, the approach was limited to the differentiation between medical and surgical jaundice. Only the initial series of liver function tests was taken into consideration and thus the duration of jaundice was not taken into account. Experiences with a group of 285 jaundiced patients served as the basis for this attempt.

This analysis had a twofold purpose: first, to develop a graphic scheme which may facilitate the recognition of the diagnostic problems in jaundice, and secondly, to evaluate empirically which liver function tests in use, with-

\* Received for publication December 2, 1947.

From the Hektoen Institute for Medical Research, the Departments of Pathology and Internal Medicine, Cook County Hospital; Department of Pathology, Northwestern University School of Medicine and the Department of Internal Medicine, University of Illinois College of Medicine, Chicago, Illinois.

Aided by a grant from the Dr. Jerome D. Solomon Memorial Research Foundation.

out reference to their physiologic basis, were, from a practical standpoint most helpful in determining the diagnosis.

### MATERIAL AND METHOD

The material studied consisted of 285 cases of various types of jaundice excluding the hemolytic variety. It included only cases in whom the diagnosis was definitely established by the follow-up course, subsequent biopsy, operation and/or necropsy findings. The patients were observed in a large general charity hospital. This is reflected by the distribution of the various types (table 1). Cirrhosis was relatively common. Acute hepatitis as well as obstructive jaundice was usually seen in somewhat advanced stages.

TABLE I  
Final Diagnoses in 285 Analyzed Cases of Jaundice

Acute Hepatitis	Cirrhosis	Benign Obstruction	Malignant Obstruction
83	122	44	36

The examined cases fell into two groups: Group I consisted of 125 cases studied between 1941 and 1943, while Group II comprised 160 cases, studied during 1946 and 1947. In the first group, the following determinations were performed: (a) total serum protein; (b) albumin-globulin ratio; (c) serum non-protein nitrogen; (d) cephalin-cholesterol flocculation<sup>10</sup>; (e) total serum cholesterol; (f) cholesterol ester/cholesterol ratio<sup>11</sup>; (g) serum alkaline phosphatase<sup>12</sup>; (h) hippuric acid synthesis after oral administration<sup>13</sup>; (i) urinary urobilinogen in a 24 hour specimen<sup>14</sup>; (j) concentration of fecal urobilinogen<sup>15</sup>; (k) plasma vitamin A<sup>16</sup>; (l) bromsulfalein retention 45 minutes after administration of 5 mg. per kg. body weight (in cases with only slight jaundice); and (m) total serum bilirubin.

In the second group, the same tests were performed with the following exceptions: the thymol turbidity was determined in all instances.<sup>17, 18, 19</sup> The hippuric acid synthesis after intravenous administration<sup>20</sup> (replacing the oral method) and the plasma vitamin A determinations were done only in selected cases; moreover, in the majority of these patients the urinary urobilinogen was determined as units in a two hour afternoon specimen.<sup>21</sup>

These examinations were supplemented with the usual clinical observation, additional laboratory studies, biopsy findings, and in some instances with the findings at operation or necropsy.

The final diagnosis was obviously not made in all cases after the primary workup because the analytical thought processes described below were not correctly applied. A number of diagnostic failures—not quite 5 per cent—occurred, many of which might have been avoided according to retrospective analysis.

The described thought processes will be composed of a number of steps. In the description of each step, two points will be made: (1) analysis of the

function tests which are taken into consideration in making this step, and (2) discussion of the cases in which this step was not justified.

### DIAGNOSTIC ROUTE

The first problem in the differential diagnosis of the jaundiced patient is the distinction between presence or absence of liver cell damage and of marked interference with the bile flow. Some interference with the bile flow is found in every patient with regurgitation jaundice. There are gradual transitions from slight interference to complete exclusion of bile from the duodenum, as is typically seen in complete extrahepatic mechanical biliary obstruction. Therefore, arbitrarily the term "marked interference with the bile flow," as used hereafter, has been defined by the results of function tests as characteristically found in established extrahepatic biliary obstruction. On this basis, in general, the patient with medical jaundice has liver cell function impairment; the patient with surgical jaundice marked interference with the bile flow.

The liver function tests used can be divided into two groups: (a) those

TABLE II  
Pathologic Levels Chosen in Liver Function Tests  
Which Are Grouped as to Their Significance

Tests Indicating			
Liver Cell Damage		Marked Bile Flow Interference	
Test	Pathologic Level	Test	Pathologic Level
Cephalin cholesterol flocculation	Above 2+	Urinary urobilinogen reduced	Less than 1.0 mg. 24 hrs. or less than 0.5 U in 2 hrs.
Thymol turbidity	Above 4 U	Fecal urobilinogen reduced	Less than 10 mg. %
Albumin-globulin ratio	Below 1.25	Serum alkaline phosphatase	Above 15 Bodansky units
Cholesterol ester/cholesterol ratio	Below 50%	Serum total cholesterol	Above 300 mg. %
Urinary urobilinogen (elevated)	Above 3 mg./24 hrs. or above 3 U in 2 hrs.		
Hippuric acid Oral test Intravenous test	Below 3 gm. Below 0.7 gm.		
Non-protein nitrogen	Above 40 mg. %		
Plasma vitamin A	Below 15 micrograms		
Bromsulfalein	Above 6% retention in 45 min. after injection of 5 mg./kg.		

which indicate liver cell damage; and (b) those which indicate marked impairment of bile flow (table 2).

The classification in table 2 agrees to some extent with that recently presented by Watson and Hoffbauer<sup>1</sup> in which the tests are divided as indicating hepatocellular or cholangiolar dysfunction. Regurgitation jaundice appears to be a cholangiolar disturbance resulting in back flow of bile through the smallest bile ducts. The previously held view that dissociation of the liver cell cords is responsible has been given up since the latter is usually a postmortem phenomenon.<sup>22</sup> Total serum bilirubin is elevated and bilirubinuria is present in every regurgitation jaundice. Though, therefore, hyperbilirubinemia and bilirubinuria appear to be due to cholangiolar dysfunction they are found in both types—in medical and surgical jaundice—and obviously from the practical standpoint are not characteristic for either group.

A decrease of prothrombin may be due to both exclusion of bile from the duodenum and liver cell damage. The prothrombin test was therefore omitted from table 2. Bromsulfalein retention may be due to both liver cell damage and marked bile flow interference. However in the presence of a mild degree of jaundice (the only time it was utilized in this series) bromsulfalein retention was only due to the former. The level of total cholesterol chosen is higher than the usually accepted pathologic borderline. However, only the high levels indicate marked bile flow interference since levels up to 300 mg. per cent are not infrequently found in other conditions. The occasional reduction of total cholesterol in hepatitis was not taken into consideration. A level of serum alkaline phosphatase between 4 and 15 Bodansky units is definitely pathologic in the adult. Such an elevation is very commonly found in all types of medical jaundice<sup>28</sup> and therefore can hardly serve as a differential diagnostic criterion between surgical and medical jaundice. Levels above 15 units have been selected since they are commonly seen in conditions in which a mechanical interference with the bile flow can be demonstrated. Since the cause of the elevation of the alkaline phosphatase level in jaundice is as yet not established, it is questionable whether the levels between 4 and 15 units represent lesser degrees of bile flow interference or liver cell damage. In contrast to the older concept that the elevation is due only to reduced excretion of alkaline phosphatase in the bile, increased formation in overstimulated pathologic liver cells has also been claimed to be responsible.<sup>24, 25, 26, 27</sup>

It is generally accepted that almost every one of the mentioned tests for liver cell damage may yield false positive results. It was, therefore, felt advisable to start under the assumption that liver cell damage is present in a jaundiced patient only if at least two of the given tests were positive. For the establishment of marked impairment of the bile flow in the presence of jaundice, one positive test was considered necessary. The correctness of these assumptions were attested by the results mentioned below.

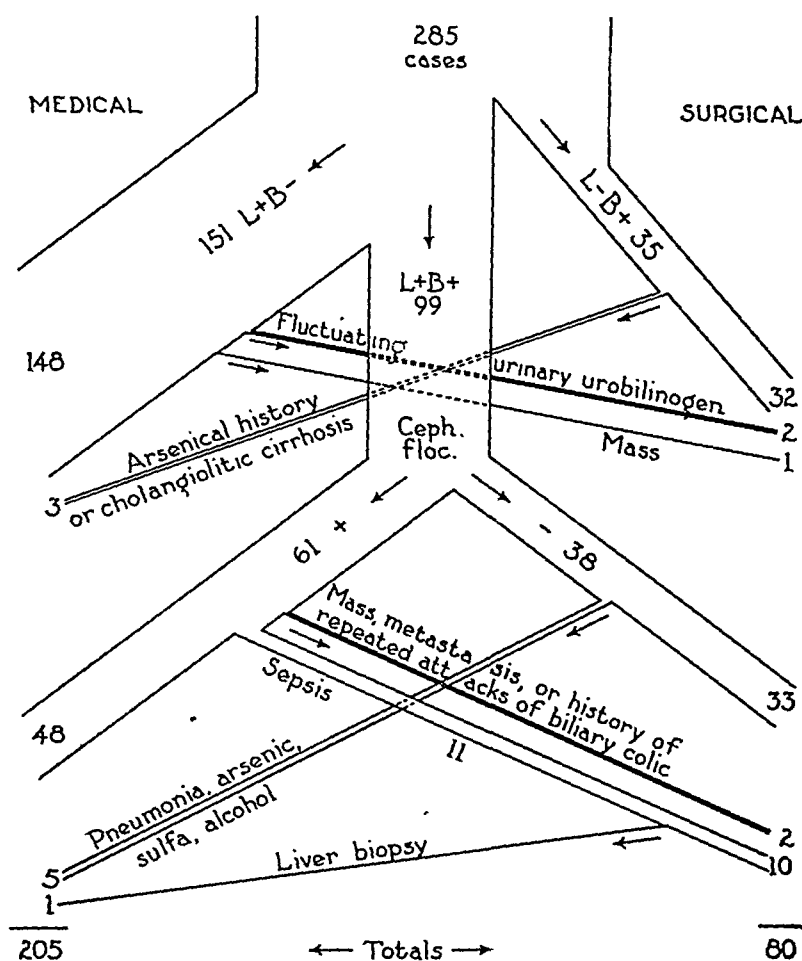


FIG. 1. Diagram demonstrating the route of the thought processes in the differential diagnosis between medical and surgical jaundice based primarily on laboratory examination. The width of the individual lanes indicates the number of cases in each. "L" indicates tests for liver cell damage; "B" tests for marked interference with bile flow.

On this basis, the cases studied were initially divided into three groups (figure 1):

- Those having liver cell damage without marked bile flow interference (L + B—) (151 cases).
- Those having marked interference with bile flow but no liver cell damage (L—B +) (34 cases).
- Those having both (L + B +) (98 cases).

*A. Cases with Liver Function Impairment but without Interference with Bile Flow.* A priori the cases of this group were considered as medical jaundice.

#### 1. Analysis of tests.

A variable number of the function tests indicating liver cell damage was positive in each individual case. Four cases in which only one test was



## Without Thymol Turbidity Test

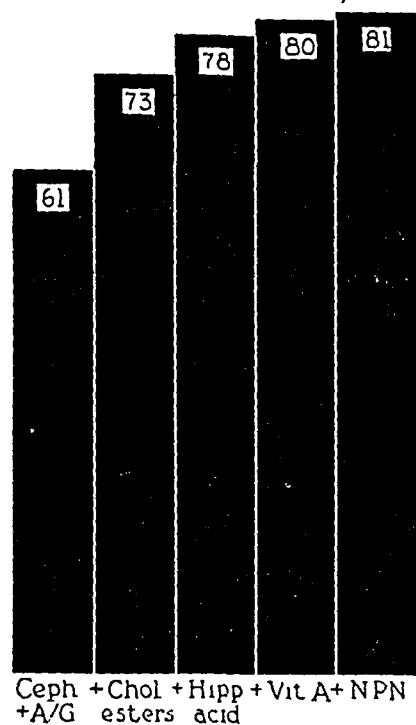
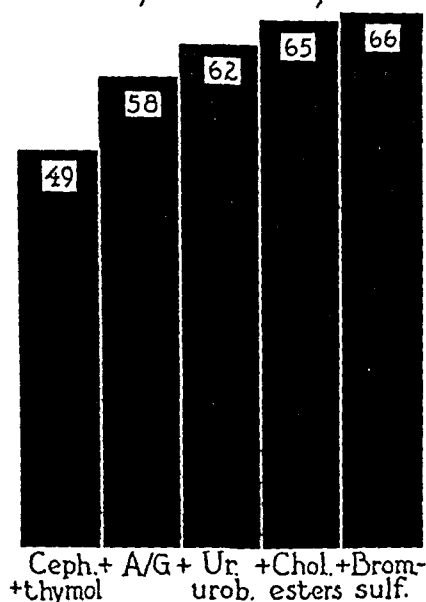


FIG. 2. Columns demonstrating the number of cases in which liver cell damage was correctly diagnosed by at least two of the listed tests. They show the increase produced by taking into account additional tests. The cases of the period 1941-1943 (without thymol turbidity test) are separated from those of 1946 and 1947 (with thymol turbidity test).

## With Thymol Turbidity Test



positive had to be included on the basis of the clinical picture. In the overwhelming majority, however, two or more tests revealed pathologic results. Most commonly three tests were positive, rarely five or six, but never more. It seems, therefore, that in the presence of jaundice one pathologic liver function test may occasionally indicate liver cell damage, but that in general, pathologic results in at least two tests should be required to indicate it.

It is not easy to decide which combination of tests is most helpful in establishing liver cell damage, since in the cases examined 67 variations in the results of the different liver function tests were encountered. The 147 cases with two or more pathologic liver function tests were divided into two groups:

- (a) 81 cases belonging to the previously described group I (without thymol turbidity test).
- (b) 66 cases belonging to group II in whom the thymol turbidity test was performed.

Six tests were necessary (cephalin-cholesterol flocculation, albumin/globulin ratio, cholesterol ester/cholesterol ratio, hippuric acid synthesis, plasma vitamin A, serum non-protein nitrogen) for the inclusion of all cases into Group I (figure 2). However, 72.8 per cent of the cases could have been accounted for by the albumin/globulin ratio and cephalin-cholesterol flocculation alone. The additional use of the cholesterol ester/cholesterol ratio increased the percentage of correct diagnosis. In only a few cases were additional tests needed.

In Group II also six tests were necessary to envelop all cases (cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio, urinary urobilinogen, cholesterol ester/cholesterol ratio and bromsulfalein retention). The majority (76.2 per cent) were correctly classified by the cephalin-cholesterol flocculation and thymol turbidity tests. The addition of the albumin/globulin ratio substantially increased the percentage of correct diagnosis (81.8 per cent) while additional tests were necessary in a few more cases.

## 2. Evaluation of diagnostic results.

Of the 151 cases comprising this group ( $L + B -$ ) 148 remained in the medical jaundice group, while three proved to be surgical in nature representing patients with incomplete obstruction and associated liver damage in whom none of the signs of marked bile flow interference were positive on admission. Two factors were diagnostically helpful in directing these three cases from the medical to the surgical group:

(a) Fluctuating urinary urobilinogen levels as found by repeated qualitative or quantitative determinations of urinary urobilinogen in two cases. It is known that in calculous jaundice the urinary urobilinogen excretion may vary on consecutive days or longer periods from diminished to highly elevated levels.<sup>28, 29</sup> In one of these two cases a negative cephalin-cholesterol flocculation was an additional support.

(b) A mass in the gall-bladder region, suggesting a hydrops of the gall-bladder on the basis of cholelithiasis, directed the third case to the surgical group.

*B. Cases with Marked Bile Flow Interference without Liver Cell Damage.* Cases characterized by marked interference with bile flow and absence of significant liver cell damage belong primarily to the group of surgical jaundice.

### 1. Analysis of tests.

In 35 cases, one or none of the tests for liver function impairment and one or more of the tests for marked interference with bile flow were positive. In the majority of the cases only one of the latter tests and only rarely all four were positive. Marked bile flow interference was indicated in the majority of the cases by a markedly elevated alkaline phosphatase. The latter test together with the absence of urinary urobilinogen accounted for almost all cases in this group. Elevated total cholesterol levels added only a few remaining cases (figure 3). Demonstration of reduced fecal urobilinogen did

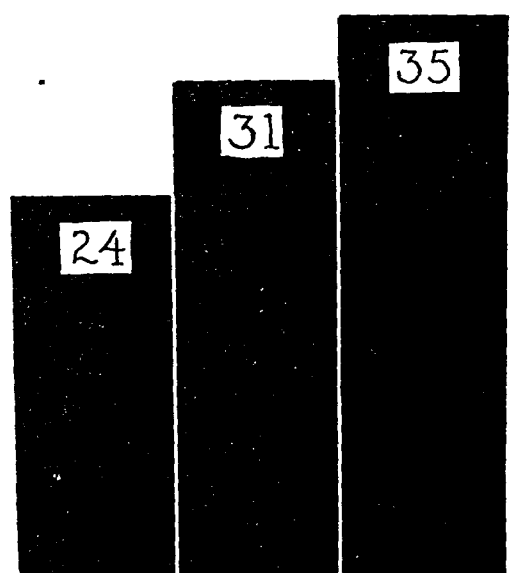


FIG. 3. Columns demonstrating the number of cases in whom marked interference with bile flow was correctly diagnosed by at least one positive test. They show the increase produced by taking into account additional tests.

Phosphat.+Ur. urob.+Cholest.

not improve the grouping of these cases since fecal urobilinogen is usually reduced when urinary urobilinogen is absent. This statement can be generalized with the exception of the rare cases in which severe renal insufficiency due to chronic glomerulonephritis with deficient filtration may cause absence of urobilinogen from urine in the presence of urobilinogen in stool.<sup>30, 31</sup> In 24 of these 35 cases, one of the tests indicating liver cell damage was also positive. The test for liver cell damage most frequently positive was reversal of the albumin/globulin ratio (11 times).

### 2. Evaluation of diagnostic results.

Of the 35 cases, 32 proved to belong to the surgical and three to the medical group. One of two factors may divert such cases to the medical side.

(a) History of Treatment with Arsenicals as Part of an Antiluetic Therapy.

After such treatment jaundice may occur which is characterized by evidence of biliary obstruction but absence of detectable liver cell damage.<sup>32</sup> This represents a fairly acute condition in which both obstruction and normal liver cell function are seen at the onset of the disease. Of the three cases in our material, belonging to this category, one had a pathologic hippuric acid synthesis, another a positive thymol turbidity, while in the third case no indication for liver cell damage was found in any of the tests performed.

(b) Cholangiolitic Cirrhosis.

According to Watson and Hoffbauer,<sup>33</sup> after the defervescence of an acute hepatitis with typical liver cell damage, a protracted condition of normal liver cell function but marked interference with bile flow may occur which they designated as cholangiolitic cirrhosis. Such cases are recognized by a careful history and evaluation of clinical and biopsy findings. We had opportunities to study cases belonging to this category, but none were observed long enough to be used in the present analysis.

*C. Cases Revealing Liver Cell Damage and Marked Interference with Bile Flow.* In the material examined, there were 99 cases in whom at least two of the tests indicating liver cell damage and one of the tests indicating marked interference with bile flow were positive. Such cases, a priori, could be due either to a primary involvement of the liver or to an extra-hepatic biliary obstruction associated with liver cell damage. In such instances, the results of the cephalin-cholesterol flocculation test served as the key criterion. This test has been described as permitting differentiation of surgical from medical jaundice in a relatively high percentage of cases since it is, as a rule, negative in the surgical group.<sup>10, 19, 34, 35, 36, 37</sup>

## I. GROUP WITH NEGATIVE CEPHALIN-CHOLESTEROL FLOCCULATION TEST

The negative cephalin-cholesterol flocculation test directed 38 cases of this group to the surgical side.

### 1. Analysis of tests.

In the majority of cases, only two of the tests indicating liver cell damage were positive (figure 4). The tests most commonly giving pathologic results were the albumin/globulin ratio, thymol turbidity and the cholesterol ester/cholesterol ratio. In most of the cases, two or three of the tests indicating marked bile flow interference were positive. In almost all of them, the serum alkaline phosphatase was markedly elevated, while urinary urobilinogen was absent in about two-thirds of the cases.

## 2. Evaluation of diagnostic results.

The presence of liver cell damage in these cases which presented both marked bile flow interference and negative cephalin-cholesterol flocculation will first suggest a biliary hepatitis, i.e., liver cell damage produced by protracted biliary obstruction.<sup>38, 39</sup> The development of biliary hepatitis depends upon the degree and the duration of the obstruction and is, there-

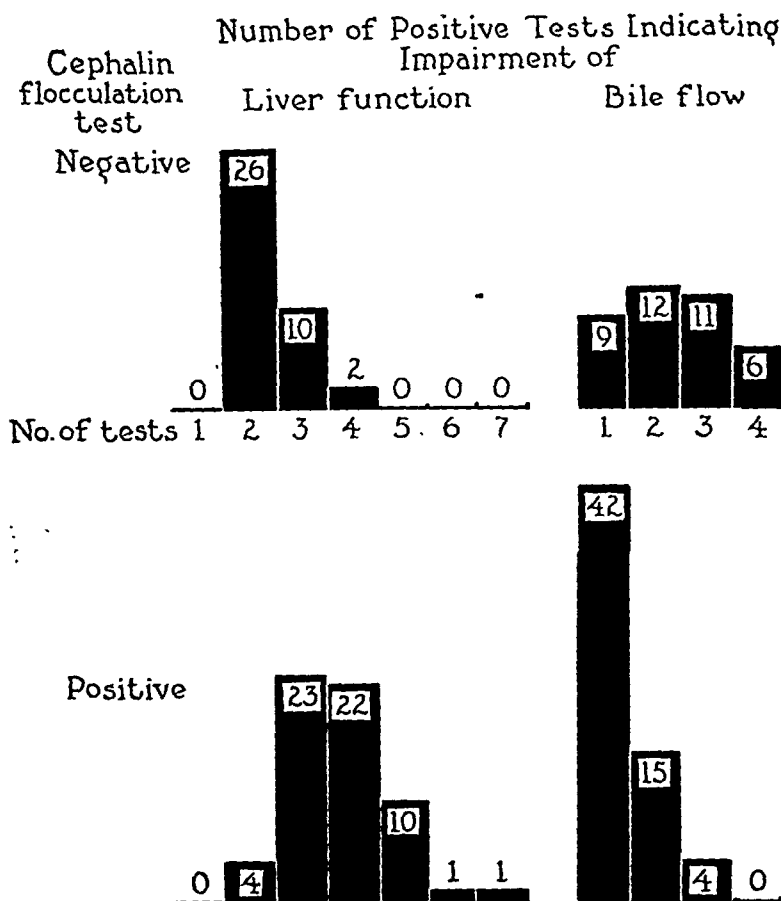


FIG. 4. Number of patients (indicated by black column) with evidence of liver cell damage and marked interference with bile flow, revealing pathologic results in a given number of liver function tests. The cases are separated according to the results of the cephalin-cholesterol flocculation test.

fore, more commonly seen in complete obstruction due to tumors than in incomplete obstruction due to stones. This is also borne out by the incidence in this series since 19 of the 33 cases remaining on the surgical side were due to malignant obstruction. Common exceptions to the rule that a negative cephalin-cholesterol flocculation is indicative of surgical jaundice are about 30 per cent of the cases of toxic hepatitis.<sup>38</sup> If in the latter, the laboratory tests indicative of marked interference with the bile flow are positive, these cases are presumptively directed into the surgical group. However, evidence of a toxic etiologic factor should direct them to the

medical side. In problematic cases, the histologic picture as seen in biopsy specimens may help in the differential diagnosis between toxic hepatitis and extrahepatic obstructive jaundice. In our material five such cases were met. Their histories revealed either exposure to arsenicals or sulfonamides, acute alcoholism, or preceding pneumonia. In all these cases, two of the tests for liver cell damage and one or two of the tests for marked bile flow interference were positive. In two of them, the non-protein nitrogen was elevated, as often seen in patients with toxic hepatitis.<sup>40</sup>

## II. GROUP WITH POSITIVE CEPHALIN-CHOLESTEROL FLOCCULATION TESTS

Positive cephalin-cholesterol flocculation diverted 61 cases to the medical side since a priori such cases should be considered as primary hepatitis with marked interference with bile flow.

### 1. Analysis of tests.

In the majority of these cases (figure 4) three or four tests indicative of liver cell damage gave pathologic results and in contrast to the previous group often five or more were positive. In addition to the cephalin-cholesterol flocculation, the albumin/globulin ratio, thymol turbidity and cholesterol ester/cholesterol ratio were most often positive. In contrast to the group with negative cephalin-cholesterol flocculation, marked bile flow interference was here primarily indicated by absence of urinary urobilinogen (46 out of 61), whereas the total serum cholesterol and serum alkaline phosphatase were less often markedly elevated.

### 2. Evaluation of diagnostic results.

Positive results of tests indicative of marked interference with the bile flow (in the presence of liver cell damage) should first suggest intrahepatic biliary obstruction as may occur in any type of acute (infectious or toxic) hepatitis or of cirrhosis. This phenomenon, at least in certain stages of hepatitis, is relatively frequent.<sup>33, 41, 42, 43</sup> However, there are certain exceptions to this assumption:

#### (a) Purulent Hepatitis.

In cases of extrahepatic mechanical biliary obstruction, either an ascending or more commonly a hemolymphatic infection of the portal triads may lead to what has been called purulent hepatitis associated with liver cell damage.<sup>38, 44</sup> This condition is not dependent upon duration or degree of the obstruction but rather upon the presence of a complicating infection. It is therefore more often a complication of benign rather than of malignant obstruction, found especially in cholelithiasis and cholecystitis. In such instances, the cephalin-cholesterol flocculation is or may become positive in a case of surgical jaundice. Obviously, such conditions will at first fall into the group of medical jaundice. They can be diverted to the surgical

side, where they belong, by the clinical evidence of a bacterial infection, i.e., fever, chills and leukocytosis, and by the typical histologic picture of the liver biopsy specimen. In our material nine cases were thus brought to the surgical side, despite liver function tests similar to those of the medical cases. One of those nine cases, despite the characteristic findings of a septicemia, did not belong in the surgical group: it represented one of the rare instances of a protracted cholangiolitis without obstruction but with transition into cirrhosis. The results of the liver biopsy as well as the fact that almost all tests indicating liver cell damage were positive brought this case back to the medical side.

(b) Biologically false positive tests.

There are rare instances of biliary hepatitis without complicating infection which have a positive cephalin-cholesterol flocculation test and which could possibly be considered as false positive. In two cases in our series such possibilities arose. They or similar ones might be correctly diagnosed by the palpatory findings in the abdomen (mass), signs of metastases, history of repeated attacks, roentgen-ray findings, etc.

#### EVALUATION OF TESTS INDICATIVE OF LIVER CELL DAMAGE

The follow-up of a large number of jaundiced patients with established diagnosis permits an evaluation of the liver function tests. It has been postulated above that in general at least two of the tests indicating liver cell damage should be positive for such damage to be entertained. This was done because practically every one of the function tests used may occasionally yield biologically false results; usually without available explanation. In four of the examined jaundice cases, however, liver cell damage had to be conceded because of clinical findings although only one of the tests for liver cell damage was positive.

The question now arises which of the tests should be selected from experience gained in practical use. Some information concerning this question was provided by the results of function tests in the above discussed smaller group of cases with liver cell damage but without marked bile flow interference. Now, all cases showing positive results in at least two tests indicating liver cell damage will be considered. These 246 cases were also divided into the two groups mentioned: Group I in which the thymol turbidity test was not performed and Group II in which this test was performed. In 135 cases of Group II (table 3) a combination of the thymol turbidity test with either the cephalin-cholesterol flocculation or the albumin/globulin ratio permitted recognition of liver cell damage in two-thirds of the cases. A combination of the cephalin-cholesterol flocculation plus the albumin/globulin ratio permitted this in a slightly smaller number. In the above percentages, results of other tests are not considered. If two positive results in all three above-mentioned tests were accepted, 83 per cent of the cases

TABLE III

Percentage of Cases with Liver Cell Damage Correctly Grouped on Basis of at Least Two Positive Tests for Liver Cell Damage, and the Increase in This Percentage Due to Inclusion of Additional Tests

With Thymol Turbidity Test	Cases Examined Per Cent	Without Thymol Turbidity Test	Per Cent
Cephalin-cholesterol flocculation plus albumin/globulin ratio.....	61.7		
Thymol turbidity test plus albumin/globulin ratio.....	66.0		
Cephalin-cholesterol flocculation plus thymol turbidity test.....	66.7	Cephalin-cholesterol flocculation plus albumin/globulin ratio.....	69.4
Cephalin-cholesterol flocculation plus thymol turbidity test plus albumin/globulin ratio*.....	83.6	Cephalin-cholesterol flocculation plus albumin/globulin ratio plus cholesterol ester/cholesterol ratio.....	84.7
The above tests plus cholesterol ester/cholesterol ratio.....	93.3	The above tests plus oral hippuric acid.....	92.8
The above tests plus urinary urobilinogen.....	98.5	The above tests plus non-protein nitrogen.....	97.3
The above tests plus bromsulfalein..	99.2	The above tests plus vitamin A....	98.2
The above tests plus oral hippuric acid	100.0	The above tests plus bromsulfalein..	99.1
		The above tests plus urinary urobilinogen.....	100.0

\* For instance pathologic results in cephalin-cholesterol flocculation and in albumin/globulin ratio but normal in thymol turbidity, or as another example all 3 being positive.

were correctly classified. The addition of the cholesterol ester/cholesterol ratio, i.e., at least two positive results in four tests, raised the percentage further to a significant degree. The additional consideration of the results of urinary urobilinogen determination, bromsulfalein retention or hippuric acid synthesis added only a few more cases. On this basis, it appears that, in the vast majority of the cases, liver cell damage can be diagnosed with four tests: cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio and cholesterol ester/cholesterol ratio. However, for correct evaluation of all of the cases in our material three more tests were necessary.

The great significance of the thymol turbidity test is indicated by comparing the above group with 111 cases of Group I which were observed before the thymol turbidity test was available. In the latter cases, the majority were "diagnosed" by the cephalin-cholesterol flocculation, the albumin/globulin ratio, the cholesterol ester/cholesterol ratio and hippuric acid synthesis whereas five additional tests were required to diagnose the remaining four cases. In our material, therefore, the thymol turbidity test reduced the number of other more complicated tests required to group the cases correctly. Additional flocculation tests may possibly further reduce the necessity for the more complicated tests and thus simplify the differential diagnosis of jaundice.



In no case were all tests indicative of liver cell damage positive (figure 5). In most instances, two to four tests were positive, whereas a higher number was rarely encountered even in severe cases.

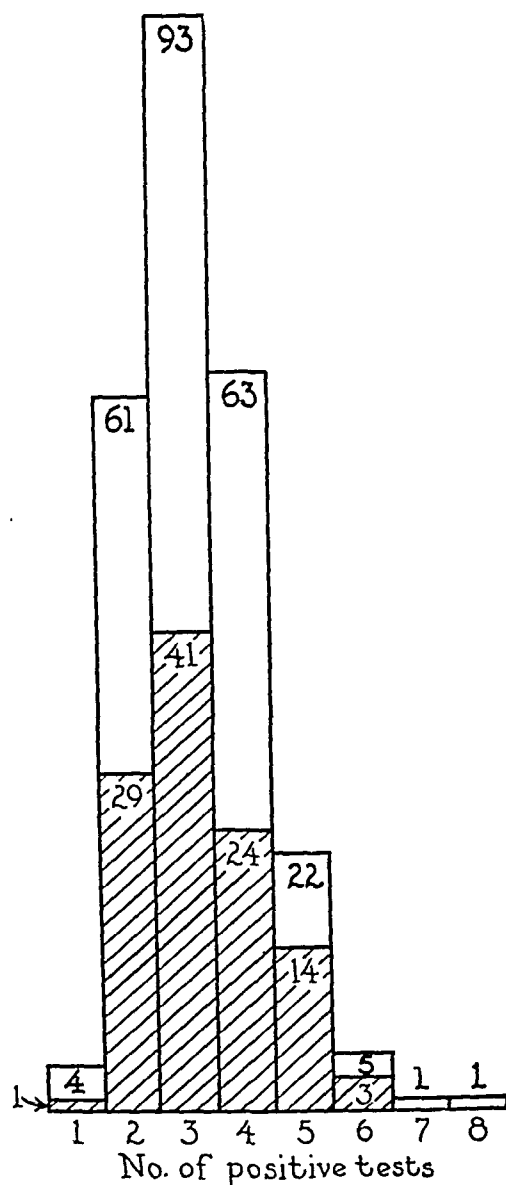


FIG. 5. Columns indicating the number of cases in whom a given number of tests indicative of liver cell damage were positive. The cross hatched part of the columns represents patients in whom no thymol turbidity tests were performed.

#### EVALUATION OF TESTS FOR MARKED BILE FLOW INTERFERENCE

One test denoting marked bile flow interference was considered sufficient to indicate that phenomenon. On this basis, the latter was diagnosed in 134 cases. In one-third of them absence of urinary urobilinogen was the only positive test; in combination with other tests, this absence was demonstrable in two-thirds of the cases (table 4). Marked elevation of the serum alkaline phosphatase alone was found in a relatively small percentage. If one positive test in the determination of either urinary urobilinogen or of serum alkaline

TABLE IV

Percentage of Cases with Marked Interference with Bile Flow Correctly Grouped on Basis of Single or Groups of Tests Denoting Marked Bile Flow Interference

Absence of urinary urobilinogen alone.....	29.8%
Serum alkaline phosphatase elevation alone.....	16.4%
Total serum cholesterol elevation alone.....	5.3%
All cases showing absence of urinary urobilinogen.....	67.1%
All cases showing absence of urinary urobilinogen and/or elevation of alkaline phosphatase.....	94.7%
All cases showing absence of urinary urobilinogen or elevated alkaline phosphatase or elevated cholesterol or combination of them.....	100.0%

phosphatase or of both was used as criterion, almost all cases of this group were accounted for. Only a few more were included because of a markedly elevated total cholesterol. In only 17 per cent of the cases were all three tests positive. The determination of the fecal urobilinogen added little in this type of analysis.

#### COMMENT

This study attempts first to analyze the thought processes used in the differential diagnosis of jaundice based primarily upon laboratory determinations, and secondly, to evaluate the liver function tests from the practical point of view by deliberately giving less emphasis to their physiologic meaning. The teaching of clinical diagnosis might be considered as the presentation of analytic thought processes which lead over various "crossings" to the correct diagnosis. In this study, an attempt was made to illustrate graphically such analytic thought processes in a case of jaundice (figure 1). The main "crossings" were provided by (1) liver cell damage, (2) marked interference with bile flow and (3) results of the cephalin cholesterol flocculation reaction in the cases in which the two former were positive. Further "crossings" were based on a history of exposure to hepatotoxic substances especially the arsenicals—pointing to a toxic hepatitis. Similarly, septic manifestations served to separate the purulent hepatitis with positive cephalin-cholesterol flocculation from primary hepatitis with marked interference with bile flow. The presence of an abdominal mass, or a history typical of biliary colics helped in the recognition of the cases in which the cephalin-cholesterol flocculation reaction might be considered as biologically false positive. In some instances, the result of the liver biopsy may be the only criterion directing the case into the right group.

As mentioned previously, we did not initially diagnose all cases correctly. Some were put in this schematic arrangement by hindsight rather than foresight. Obviously, even in following the described lines, one may not always reach the correct diagnosis at first.

In evaluating liver function tests, one should be aware of the fact that almost every one of them may occasionally yield a pathologic result if done on a large series of so-called normal controls. Such pathologic results have to be considered biologically false positive since no other evidence for liver function impairment exists, either on the basis of clinical or other laboratory

examination. There is probably a biologic reason for the positive results in such instances, but it is apparently not related to the liver. This reason may be obvious in instances of pathologic albumin/globulin ratio or non-protein nitrogen levels, but is usually obscure in the case of cephalin-cholesterol flocculation or thymol turbidity. The term biologically false positive is used in analogy with the sero-diagnosis of syphilis where it applies to positive reactions in the absence of syphilis. According to the presented concept, the cephalin-cholesterol flocculation reaction is negative in obstructive jaundice with and without biliary hepatitis, except in the purulent form. It is positive in most types of primary hepatitis and cirrhosis. To allow for biologically false positive results, consideration of an abdominal mass, or typical history had to be introduced. Moreover, the possibility of biologically false positive tests was the reason for insisting on two positive tests as indicative of liver cell damage. It should be stressed that not too often were more than three tests for liver cell damage positive, even in quite severe cases of hepatitis. Similarly only in relatively few instances were all tests indicating marked bile flow interference positive.

The number of positive tests in a patient without consideration for their individual physiologic basis is apparently of some significance. The higher the number of positive tests the more marked is the liver cell damage. As long as the physiologic basis for many of the tests remains obscure, such an assumption may be helpful. Thus, for instance, in the group in which both liver cell function and bile flow were impaired, the sub-group with positive cephalin-cholesterol flocculation, which as a whole presents primarily medical jaundice, had a much higher number of positive tests than the sub-group with negative flocculation in which biliary hepatitis is prominent. In the latter group more of the tests indicating marked bile flow interference were positive, whereas in the former group, only urinary urobilinogen was absent in most instances. Since this absence is only temporary, serial observations of urobilinogen excretion would eliminate many cases from this group and line them up with uncomplicated cases of medical jaundice which showed only liver cell damage on admission.

There may also be biologically false positive results in the tests indicating marked bile flow interference. Obviously, the total cholesterol may be elevated due to reasons not connected with the jaundice and the serum alkaline phosphatase may be markedly increased, e.g., due to bone lesions. However, these factors are readily recognized by clinical observation. In the presence of jaundice, therefore, one positive test for marked bile flow interference is sufficient, provided other disturbing factors are taken into account.

In reviewing the entire material, one is struck by the frequent concurrence of both liver cell damage and marked bile flow interference (34.7 per cent of the cases). This indicates that the usually held premise from which this study also started, namely, that medical jaundice has only liver cell damage, and surgical jaundice as a rule only marked bile flow interference

is incorrect in a significant number of cases. Of the medical cases, 26.3 per cent were complicated by marked interference with the bile flow, something of the nature of what has been previously called intrahepatic biliary obstruction. In the majority of cases with surgical jaundice (60 per cent) liver cell damage was found. The latter was due in 47.5 per cent to biliary hepatitis (secondary liver cell damage due to prolonged obstruction) and in 12.5 per cent to purulent hepatitis caused by bacterial infection of the portal triads. Nevertheless, the above-mentioned premise proved to be a good starting point for a diagnostic analysis.

On the basis of the material presented here, the performance of the following liver function tests can be recommended for the differential diagnosis between medical and surgical jaundice: cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio, cholesterol ester/cholesterol ratio, urinary urobilinogen and serum alkaline phosphatase. To group all cases, it may be advantageous to add the bromsulfalein retention and the hippuric acid synthesis.

Obviously, more laboratory determinations than these considered in this study are in clinical use, e.g., urinary and serum bilirubin, galactose tolerance test, total serum protein (especially for control of therapy), urinary amino acid excretion, prothrombin time and sedimentation rate. They give important information and may determine the diagnosis in some patients. Most of them were determined in our cases, but were omitted from the discussion for the sake of simplicity. It should also be stressed that only the initial determination was taken into account and that, for instance, the follow-up of the serum bilirubin concentration was not taken into consideration. Similarly, the degree of alteration from the normal was not considered. Thus the thymol turbidity, although positive in a significant number of cases of surgical jaundice, seldom rises above 10 units in the latter condition, in contrast to medical jaundice.

#### SUMMARY

It is attempted to present a schematic plan of the thought processes applied in the differential diagnosis between medical and surgical jaundice. It uses primarily laboratory findings but takes into account, to some extent, clinical history and/or physical findings. It is based primarily upon the recognition of liver cell damage and marked interference with the bile flow. The cases revealing both are further subdivided by the results of the cephalin-cholesterol flocculation test.

The analysis of these thought processes provides an opportunity for evaluating the efficiency of the liver function tests for practical purposes without emphasis upon their physiological basis. It appears that at least two positive tests are necessary to establish liver cell damage, but only one to recognize marked bile flow interference. Only rarely are all tests indicating either of the two phenomena positive and the number of positive tests appears to parallel the severity of the pathologic process.

The overwhelming majority of cases will be guided into the right direc-

tion if cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio, total serum cholesterol, and cholesterol esters, serum alkaline phosphatase and urinary urobilinogen are determined. The addition of the hippuric acid synthesis and bromsulfalein retention tests permitted, in the final evaluation, correct grouping of all cases in this series.

The addition of the thymol turbidity test has markedly decreased the need for the more complicated liver function tests in the differential diagnosis of jaundice. It may, therefore, be expected that additional flocculation or precipitation tests may further simplify the laboratory diagnosis of jaundice.

### BIBLIOGRAPHY

1. WATSON, C. J., and HOFFBAUER, F. W.: Liver function in hepatitis, *Ann. Int. Med.*, 1947, xxvi, 813.
2. ROSENBERG, D. H., and SOSKIN, S.: Comparison of the cephalin cholesterol flocculation test with various criteria of liver function, *Am. Jr. Digest. Dis.*, 1941, viii, 421.
3. GUTMAN, A. B., and HANGER, F. M., JR.: Differential diagnosis of jaundice by combined serum phosphatase determination and cephalin flocculation test, *Med. Clin. North Am.*, 1941, xxv, 837.
4. STEIGMANN, F., POPPER, H., and MEYER, K. A.: Liver function in clinical medicine, *Jr. Am. Med. Assoc.*, 1943, cxxii, 279.
5. IVY, A. C., and ROTH, J. A.: Why do liver function tests? *Gastroenterology*, 1943, i, 655.
6. SCHWIMMER, D., KLOTZ, S. D., DREKTER, I. J., and MCGAVACK, T. H.: A fasting-blood-sample procedure in the differential diagnosis and management of hepatic disease, *Am. Jr. Digest. Dis.*, 1945, xii, 1.
7. TEITELBAUM, M., CURTIS, A. C., and GOLDHAMER, S. M.: The comparative value of several liver function tests, *Ann. Int. Med.*, 1945, xxii, 653.
8. MATEER, G., BALTZ, J. I., COMANDURAS, P. D., STEEL, H. H., and BROUWER, S. W.: Further advances in liver function tests and the value of a therapeutic test in facilitating the earlier diagnosis and treatment of liver impairment, *Gastroenterology*, 1947, viii, 52.
9. SNELL, A. M.: The management of jaundiced patients, *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 1175.
10. HANGER, F. M.: Serologic differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin cholesterol emulsion, *Jr. Clin. Invest.*, 1939, xviii, 261.
11. KRAUS, I., and KALAL, E.: Effect of standing on cholesterol and cholesterol ester values in human blood, *Jr. Lab. and Clin. Med.*, 1942, xxvii, 1208.
12. BODANSKY, A.: Phosphatase studies: determination of serum phosphatase: factors influencing accuracy of determination, *Jr. Biol. Chem.*, 1933, ci, 93.
13. QUICK, A. G.: Synthesis of hippuric acid; new test for liver function, *Am. Jr. Med. Sci.*, 1933, clxxxv, 630.
14. WATSON, C. J.: Studies of urobilinogen. I. An improved method for the quantitative estimation of urobilinogen in urine and feces, *Am. Jr. Clin. Path.*, 1936, vi, 458.
15. STEIGMANN, F., and DYNIEWICZ, J. G.: Studies of urobilinogen. The daily urobilinogen excretion in urine and feces in health and disease: an evaluation of Watson's and Sparkman's method, *Gastroenterology*, 1943, i, 743.
16. POPPER, H., and STEIGMANN, F.: The clinical significance of the plasma vitamin A level, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 1108.
17. MACLAGAN, N. F.: Thymol turbidity test: A new indicator of liver dysfunction, *Nature*, London, 1944, cliv, 670.
18. MACLAGAN, N. F.: The thymol turbidity test as an indicator of liver dysfunction, *Brit. Jr. Exper. Path.*, 1944, xxv, 234.
19. WATSON, C. J., RAPPAPORT, E. M., HAWKINSON, V., and GIEBENHAIN, M.: A com-

- parison of the results obtained with the Hanger cephalin-cholesterol flocculation test and the MacLagan thymol turbidity test in patients with liver disease, *Jr. Lab. and Clin. Med.*, 1945, xxx, 983.
20. QUICK, A. J.: Clinical application of hippuric acid and prothrombin tests, *Am. Jr. Clin. Path.*, 1940, x, 222.
  21. WATSON, C. J., SCHWARTZ, S., SBOROV, V., and BERTIE, E.: A simple method for the quantitative recording of the Ehrlich reaction as carried out with urine and feces, *Am. Jr. Clin. Path.*, 1944, xiv, 605.
  22. POPPER, H.: The significance of agonal changes in the human liver, *Arch. Path.*, in press.
  23. GUTMAN, A. B., OLSON, K. B., GUTMAN, E. G., and FLOOD, C. A.: Effect of disease of the liver and biliary tract upon the phosphatase activity of the serum, *Jr. Clin. Invest.*, 1940, xix, 129.
  24. DRILL, V. A., ANNEGERS, J. A., SNAPP, E. F., and IVY, A. C.: Effect of biliary fistula on bromsulphalein retention, serum phosphatase, and bile phosphatase, *Jr. Clin. Invest.*, 1945, xxiv, 97.
  25. RAPOPORT, S.: Increased serum phosphatase and "hyperprothrombinemia" in infectious hepatitis of children, *Proc. Soc. Exper. Biol. and Med.*, 1946, lvii, 203.
  26. OPPENHEIMER, M. J., and FLOCK, E. V.: Alkaline phosphatase levels in plasma and liver following partial hepatectomy, *Am. Jr. Physiol.*, 1947, cxlix, 418.
  27. FREEMAN, S., CHEN, Y. P., and IVY, A. C.: On the cause of elevation of serum phosphatase in jaundice, *Jr. Biol. Chem.*, 1938, cxxiv, 79.
  28. WATSON, C. J.: Studies of urobilinogen: per diem excretion of urobilinogen in common forms of jaundice in disease of liver, *Arch. Int. Med.*, 1937, lix, 206.
  29. STEIGMANN, F. and DYNIEWICZ, J. M.: Studies of urobilinogen. II. Quantitative urobilinogen determination in the differential diagnosis of jaundice, *Gastroenterology*, 1943, i, 855.
  30. OLIVA, G., and MASSIMELLO, F.: Sulla ritenzione urobilinemica nelle nefropatie, *Arch. per le sci. med.*, 1935, lix, 467.
  31. WATSON, C. J.: Cirrhosis of the liver: clinical aspects with particular reference to liver function, *Am. Jr. Clin. Path.*, 1943, xiii, 129.
  32. HANGER, F. M., and GUTTMAN, A. B.: Postarsphenamine jaundice apparently due to obstruction of intrahepatic bile tract, *Jr. Am. Med. Assoc.*, 1940, cxv, 263.
  33. WATSON, C. J., and HOFFBAUER, F. W.: The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver, *Ann. Int. Med.*, 1946, xxv, 195.
  34. ROSENBERG, D. H.: The cephalin-cholesterol flocculation test in cases of disease of the liver, *Arch. Surg.*, 1941, xliii, 231.
  35. KIRSCHNER, P. A., and GLICKMAN, S. I.: The cephalin flocculation test in jaundice, *Jr. Lab. and Clin. Med.*, 1943, xxviii, 1721.
  36. NADLER, S. B., and BUTLER, M. F.: The cephalin-cholesterol flocculation test in the jaundiced patient, *Surgery*, 1942, xi, 732.
  37. YARDUMAIN, K. Y., and WEISBAND, B. J.: The cephalin cholesterol flocculation test in liver disease, *Am. Jr. Clin. Path.*, 1943, xiii, 382.
  38. POPPER, H., and FRANKLIN, M.: Differential diagnosis of hepatitis by histologic and functional laboratory methods, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 230.
  39. MACMAHON, H. E., and MALLORY, F. B.: Obstructive cirrhosis, *Am. Jr. Path.*, 1929, v, 645.
  40. POPPER, H., and FRANKLIN, M.: Viral vs. toxic hepatic necrosis, *Arch. Path.*, in press.
  41. STEIGMANN, F., and POPPER, H.: Intrahepatic obstructive jaundice, *Gastroenterology*, 1943, i, 645.
  42. LICHTMAN, S. S.: Diseases of the liver, gall bladder and bile ducts, 1942, Lea & Febiger, Philadelphia.
  43. STEIGMANN, F., MEYER, K. A., and POPPER, H.: Marked interference with bile flow in hepatitis, *Arch. Surg.*, in press.
  44. MACMAHON, H. E.: Infectious cirrhosis, *Am. Jr. Path.*, 1931, vii, 77.

# LOEFFLER'S SYNDROME AND PULMONARY INFILTRATIONS ACCOMPANIED BY PERIPHERAL EOSINOPHILIA \*

By JOHN C. HAM, M.D., and WALTER T. ZIMDAHL, M.D.,  
*Northampton, Massachusetts*

IN the past several years reports have appeared in the American literature on patients with pulmonary infiltration accompanied by blood eosinophilia. In 1932 Loeffler<sup>1</sup> first described a syndrome characterized by these two signs. By 1940, 105<sup>2</sup> cases had been reported in the literature, 51 of these by Loeffler.<sup>3</sup> Most of the cases since then have come from the central European area. In 1945, Miller<sup>4</sup> reported one case and could find but four similar cases reported<sup>2, 5, 6, 7</sup> in this country. More and more attention has been given recently to pulmonary infiltrations with blood eosinophilia, climaxed by an editorial in the *Journal of the American Medical Association*.<sup>8</sup> However, there has been a general tendency to associate any case having pulmonary infiltrations and blood eosinophilia with the syndrome described by Loeffler.

Loeffler's original description is worthy of note. The principal finding is a pathological shadow in the roentgenogram of the chest. This is variable and may be bilateral or unilateral, large or small, simple or multiple, homogeneous or spotty. It may appear at any site and have any extent. The most important feature is its fleeting character. It decreases in size and intensity in from three to eight days. Other similar shadows may appear in different regions of the lungs in rapid succession.

The eosinophilia varies widely from very slightly above normal to 60 per cent in some cases. The degree of eosinophilia and extent of the pulmonary changes show no parallelism. The height of the eosinophilia tends to occur after the maximal pulmonary infiltrations. Over 25 per cent of Loeffler's cases were discovered on routine roentgenographic examination. As a rule the patients have few and minor symptoms, and only slight elevation of temperature. Over 60 per cent of the patients were entirely afebrile in Loeffler's series. Cough is relatively frequent and can be severe. Sputum is usually absent or slight with mucoid, frothy consistency. A small pleural effusion or friction rub has at times given evidence of occasional pleural involvement, which would explain the occurrence of chest pain. Abnormal physical signs over the lung fields are few and in general consists of occasional moist râles. Some seasonal incidence is noted in that most of the cases were found in July and August. The course is always benign. The patients usually do not suffer more than slight disturbances of their general condition.

\* Received for publication May 26, 1947.

From the Medical Service of the Rhode Island Hospital, Providence, Rhode Island.

An adequate explanation of the etiology and pathological picture is lacking. Loeffler believed that the eosinophilia could not be considered either as an expression of an anaphylactic process or the result of parasitic infection. He likewise discarded the assumptions of some authors that the lung changes were due to emboli, localized bronchial asthma, or atelectasis. He said that at times the infiltrations are differentiated only with difficulty from early tuberculous infiltration or from genuine pneumonia, and he emphasized that repeated roentgenograms were necessary to make a diagnosis. In none of his cases was tuberculosis demonstrated, although one of his cases developed tuberculosis one year later. In 35 per cent of his cases the tuberculin test was negative. He emphasized five characteristics of the syndrome: (1) infiltrations shown by roentgenogram, (2) fleeting and changing character, (3) eosinophilia, (4) mild degree of illness, (5) short duration.

We have observed three cases recently with pulmonary infiltrations and blood eosinophilia. All of them showed interesting clinical findings.

#### CASE REPORTS

*Case 1.* E. B., a 19 year old white student nurse, was first admitted to the Rhode Island Hospital April 4, 1944 with the chief complaint of malaise and headache of eight hours' duration. There was no history of any chest pain, sore throat or cough. Past history was entirely negative.

Family history revealed that her brother and sister had had symptoms of hay fever during the months of August and September for the past three years.

Review of systems was non-contributory.

*Physical Examination.* Blood pressure was 110 mm. Hg systolic and 80 mm. diastolic, temperature 100.2° F., pulse 128, respirations 28. The patient was a well-developed and well-nourished white female in no apparent distress, holding an icebag to her head. The pharynx was slightly injected. There were a few posterior cervical glands palpable. The lungs were clear to auscultation and percussion. The heart was not enlarged and showed a regular mild tachycardia. Her skin was warm and moist, and a diagnosis of mild influenza was made.

*Laboratory Data* (day of admission). Urine: Specific gravity 1.018, contained no red blood cells, a few white blood cells, no casts, albumin and sugar negative. Blood: White blood cells 27,000 (87 per cent neutrophils, 4 per cent lymphocytes, 8 per cent monocytes, 1 per cent eosinophiles), 4,610,000 red blood cells, blood urea nitrogen 16 mg. per cent.

*Hospital Course.* The patient experienced a bad initial night and developed a dry, hacking cough. Her temperature rose to 102° F. Examination of the lungs revealed medium crepitant râles in the left upper posterior chest. Later on the same day, the patient appeared moderately ill, and became dyspneic. Examination of the chest at this time revealed crepitant râles which were heard over both anterior chests, more pronounced in the upper right. The white blood count had risen to 31,950. A roentgenogram of the chest (figure 1) revealed extensive density throughout both lungs, most marked at the bases, and consistent with a diffuse pneumonitis. There was no fluid present in the pleural cavities. The diaphragm and heart shadow appeared normal. A blood culture and sputum examination were obtained and the patient was started on sodium sulfadiazine five grams by mouth. This instituted vomiting, the sulfadiazine was discontinued, and sulfamerazine was given, one gram every four hours.



On the third hospital day the patient was somewhat irrational. Her temperature rose to 103° F., pulse 140, and respirations 40. During the afternoon she suddenly had a severe attack of dry, hacking cough, cyanosis and dyspnea. She was put immediately into a Burgess oxygen tent with some relief. Nose and throat cultures revealed no pathogenic organisms. Her white count, at this time, was 30,250, with 88 per cent neutrophiles. The sputum was negative for pneumococcal typings.

On the fourth hospital day sputum examination remained negative. Sulfamerazine blood level was 12.93 mg. per cent. A repeat roentgenogram of the chest showed



FIG. 1. Roentgenogram of chest in Case 1. It showed extensive density throughout both lungs most marked at the bases.

findings much the same as in the previous one, with a diagnosis of an acute bronchopneumonia. The patient continued to have a dry, hacking cough and became more dyspneic. During that night she suddenly became very cyanotic, apneic and appeared lifeless. Artificial respiration was immediately started and continued for a length of time necessary to prepare 20 c.c. of a solution containing 7.5 grains of aminophylline. This was given intravenously, and after about 15 c.c. had been injected, the patient suddenly started to breathe spontaneously. Oxygen under positive pressure and a helium-oxygen mixture were tried but the patient did not tolerate either. She was kept in an oxygen tent. Examination of the chest continued to reveal fine râles which shifted

On the sixth hospital day she began to raise a little mucoid sputum, sometimes blood-tinged. This showed no pathogenic organism on culture or smear. A portable roentgenogram of the chest (figure 2) showed accentuation of the lung markings and diffuse mottled density throughout both lungs with marked increase in the process compared with that of the previous films. The white cell count was 22,250, with 88 per cent neutrophils, 7 per cent lymphocytes, 2 per cent monocytes, and 3 per cent eosinophiles. On the seventh hospital day it increased to 31,800, with 89 per cent



FIG. 2. Roentgenogram of chest in Case 1 on the sixth hospital day. It showed accentuation of the lung markings and a diffuse, mottled density throughout both lungs with a marked increase in the process compared to previous films

neutrophils (table 1). Her temperature had remained elevated throughout her course in spite of sulfonamide therapy. Repeated blood cultures remained sterile. Examination of the lungs showed high pitched breath sounds and coarse râles at the right base especially in the axilla, with diminished breath sounds over the left lower posterior chest. On the eighth hospital day the white count remained elevated but with an increase of eosinophiles to 10 per cent. Agglutination tests were negative for typhoid O and H, paratyphoid A and B, undulant fever, and proteus OX19

TABLE I  
Summary of Data

Date	Temperature F.	White Cell Count	Neutrophils %	Differential Count		Eosinophiles %	Sedimentation Rate mm. per hour
				Lymphocytes %	Monocytes %		
4/ 5/44	102.0°	27,700	87	4	8	1	48
4/ 7/44	103.0°	30,250	88	10	2	0	
4/11/44	101.0°	31,800	89	10	1	3	
4/12/44	102.4°	25,800	80	10	0	10	
4/15/44	98.6°	23,300	43	12	2	41	
4/17/44	98.8°	14,950	68	12	2	18	
4/21/44	98.8°	7,950	60	28	5	7	
5/ 2/44	98.8°	9,900	57	31	7	5	34
<i>2nd Admission</i>							
5/17/44	102.0°	18,600	84	12	4	0	10
		10,150				0	
<i>3rd Admission</i>							
10/30/45	99.0°	16,900	70	24	5	1	40
11/ 2/45	100.6°	14,250	70	16	13	1	
11/ 3/45	102.6°	17,250	71	16	9	4	
11/ 8/45	103.0°	23,150	81	19	0	0	
11/16/45	98.6°	9,600	65	28	6	1	11

On the ninth hospital day the patient was somewhat disoriented. Her temperature was 102.4° F. During the afternoon she had a second sudden attack of apnea and cyanosis which was again relieved by 7.5 grains of intravenous aminophylline. Examination of the lung fields showed dullness, harsh breath sounds, and diminished vocal and tactile fremitus over the right lower lobe, posteriorly. Repeat examination of the chest by roentgenogram still showed extensive increased density throughout both lungs and in comparison with the previous films showed some clearing of the process. There was no evidence of fluid in the pleural cavities.

On the eleventh hospital day the patient's white count was 23,300, with 43 per cent neutrophils, 12 per cent lymphocytes, 2 per cent monocytes, 41 per cent eosinophiles. A nasal smear revealed 10 to 12 eosinophiles per high dry field.

On the fifteenth day a repeat examination of the chest by roentgenogram showed a diffuse cloudy opacity and mottled infiltration throughout both lungs, but there was a continued clearing and improvement of the process in comparison with the previous films.

On the seventeenth hospital day the white count was 7950, with 7 per cent eosinophiles. She was taken out of oxygen and continued to improve and feel much better. On the twentieth hospital day her temperature returned to normal. Sulfamerazine was discontinued on the twenty-second hospital day. Patient continued to improve and examination of the lung fields at this time showed no abnormalities. However, repeat roentgenographic examination showed accentuation of the hilar shadows and cloudy opacity in the lower halves of both lung fields. Comparison with the previous films showed considerable clearing of the process.

Sedimentation rate at this time was 34 mm. in one hour, and her white count had dropped to 9900, with 5 per cent eosinophiles. The patient improved and was discharged on the forty-first hospital day. Examination of the chest by roentgenogram (figure 3) at this time showed slight accentuation of the hilar shadows and markings, but the lung fields were clear and showed no residual density or other pathologic

process. Repeated sputum examinations were negative for acid fast bacillus; skin tests for tuberculosis and brucellosis were negative, as were stools for ova and parasites.

Second Hospital Admission: The patient was readmitted May 16, 1944. One day previous she had weakness and went to bed. Her temperature was 100.8° F.

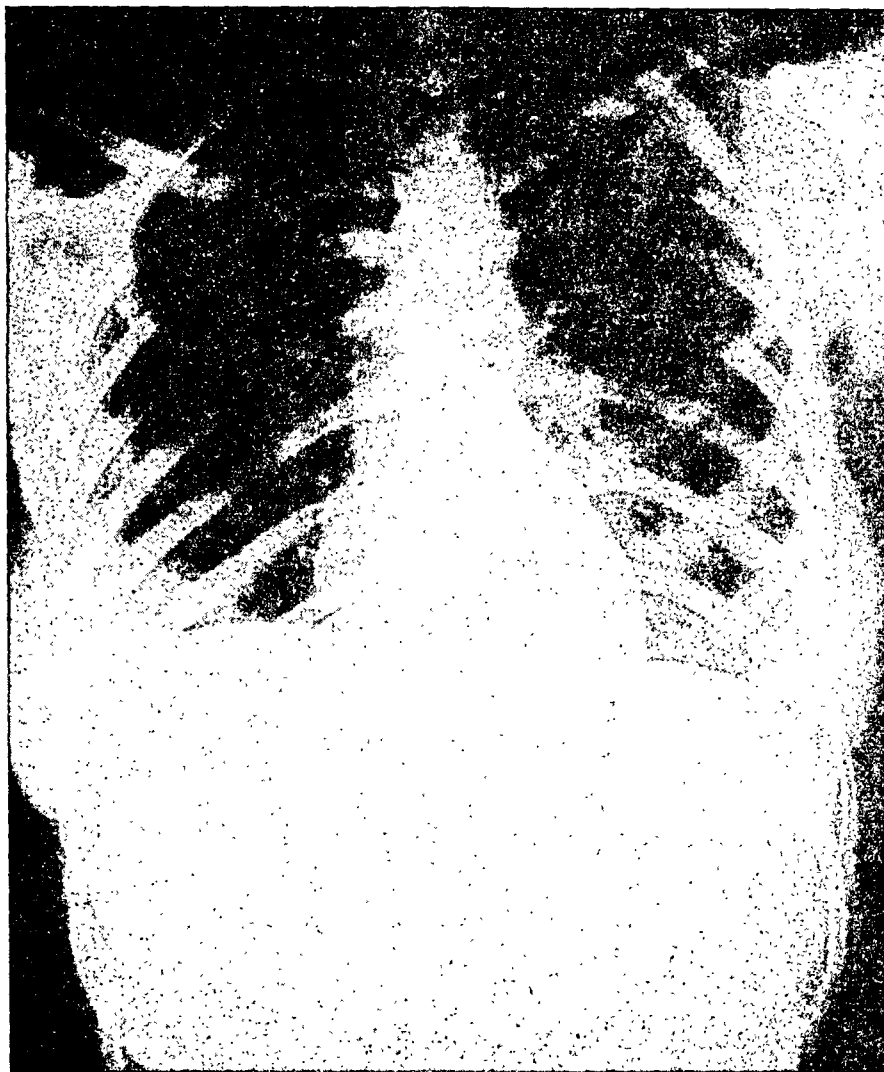


FIG. 3. X-ray of chest of Case 1 on fortieth hospital day. It showed slight accentuation of the hilar shadows and markings but the lung fields were clear.

She felt similar to her previous admission, with malaise, headache, and generalized aching.

Physical examination at this time was essentially negative.

*Laboratory Data.* Her white blood count at this time was 18,900, with 84 per cent neutrophils, 12 per cent lymphocytes, and 4 per cent monocytes. Temperature on admission was 102° F. Roentgenogram of the chest showed clear lung fields with no evidence of recurrence or residual density in the lungs. Blood culture was sterile and a repeat white blood count was 10,150 with no eosinophiles. Electro-

cardiogram showed a slight sinus arrhythmia. Rate was 112. Conduction time was within normal limits. The T-waves were all upright except T<sub>3</sub> which was diphasic. Chest fluoroscopy at this time showed the lung fields to be clear and diaphragmatic excursions and cardiac silhouette within normal limits. Skin tests with 24 common allergens at this time were negative. The patient improved and was discharged.

Third Hospital Admission: October 30, 1945.

*Interval Note.* The patient had been in good health since her last hospitalization until 48 hours before present admission. At that time she began to feel tired and had a mild sore throat which gradually became worse. She developed a cough productive of small amounts of greenish and brownish sputum. She had no chills or noticeable fever, and no pain in her chest. The patient developed a headache on the day of admission. She noticed some pain on swallowing.

Physical examination showed a well-developed, well-nourished woman in no acute distress. She was coughing occasionally. Temperature 99.6° F., pulse 90, respirations 24. Except for moderate injection of the posterior pharynx, the physical examination was essentially negative. The lungs were normal to examination, and no râles were heard.

*Laboratory Data* (on admission). Urine was normal. Blood: White blood count 16,900, with 70 per cent neutrophils, 24 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles. Hemoglobin 15 grams, glucose 74 mg. per cent.

A chest roentgenogram showed in the left upper lung field a small patch of faint haziness at the level of the third rib anteriorly, and localized somewhat laterally. The remainder of both lung fields was clear.

On the second hospital day her temperature rose to 100.6° F. She was coughing rather severely and still complained of pain on swallowing. The pharynx was moderately injected. She was started on 20,000 units of penicillin every two hours intramuscularly. Her temperature remained elevated, and the patient had difficulty in swallowing because of pain. The chest revealed no abnormalities by percussion and auscultation. The white count was 14,250, with 70 per cent neutrophils. A throat culture was negative for hemolytic streptococcus. Penicillin was discontinued at this time. A repeat chest roentgenogram showed the right lung field clear throughout. On the left side there was some faint patchy haziness in the upper lung extending from the level of the second rib to the third interspace anteriorly. The remainder of the fields was clear. The appearances in the left side were interpreted as being consistent with an atypical bronchopneumonia. Sheep cell agglutinations were negative. At this time the patient did not seem very ill. Numerous crepitant râles were heard over both lower lung fields on the ninth hospital day. On the tenth day her white count was 23,150, with an increase in neutrophils to 81 per cent. A roentgenogram in comparison with the previous one taken November 2, 1945, showed some mottling throughout the lower half of the right lung field. Similar fine mottling was seen throughout the left lung lobe in addition to practically the same irregular patches of peripheral haziness previously noted in the upper left field.

During the next five days her temperature remained normal. Examination of the chest revealed much clearing, although scattered râles over both bases were still present. She continued to improve and was discharged. The chest roentgenogram two months later showed no residual pathological signs. During the next year she remained free of all symptoms and her chest roentgenogram remained negative.

*Case 2.* H. N., a 49 year old white cook, was admitted to the Rhode Island Hospital June 9, 1945. The patient's present illness dated back about two months when she noticed a pain in her upper chest on such exertion as going upstairs and going about her duties as cook. She had also noted marked shortness of breath on exertion. Her appetite had been poor and she had a mild non-productive cough. These symptoms had become progressively worse and the location of the pain had become centered in the precordial area with radiation into the neck.

Past history was essentially negative. She had always been an active and apparently healthy individual.

Family history was essentially negative.

Review of systems was essentially normal except for present illness.

Physical examination revealed a well-developed, well-nourished woman not appearing ill. Her color was good and respirations were quiet. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic, temperature 101.6° F., pulse 100, respira-



FIG. 4. Initial roentgenogram of chest in Case 2. It showed thickened markings at the base of the right lung with dense streaks projecting laterally over the axillary portion of the ninth rib. On the left side there was a patchy, irregular density through the middle two-thirds of the lung from the fifth interspace to the ninth rib posteriorly.

tions 24. Her pupils were round and regular and reacted to light. The throat was not injected. Her tongue was slightly coated. The heart was slightly enlarged to percussion. The first sound at the apex was somewhat accentuated and snapping and there was a soft systolic murmur at the apex. No diastolic murmurs could be heard. The abdomen was lax, with no masses, spasm, or tenderness. Her lungs were clear and resonant throughout.

*Laboratory Data* (on admission). Red blood count 4,080,000, hemoglobin 12.9 gm., white blood count 14,900, with 32 per cent neutrophils, 23 per cent lymphocytes,

42 per cent eosinophiles. Blood urea nitrogen 8 mg. per cent. Agglutination tests were negative for typhoid H and O; paratyphoid A and B; undulant fever and proteus OX19. The sputum showed no acid fast organisms. A roentgenogram of the chest (figure 4) showed mild enlargement of the left ventricle of the heart. The aortic arch was negative. At the base of the right lung there were thickened markings with some dense streaks projecting laterally over the axillary portion of the ninth rib. On the left side there was a patchy, irregular density through the middle two-thirds of the lung from the fifth interspace to the ninth rib posteriorly. The markings in this neighborhood were irregularly thickened. The basal portion of the lung was negative. The interpretation was that this was consistent with a recent pneumonic process. The possibility of neoplasm could not be excluded. The shadow in the right base was suggestive of a healing infarct.

*Course in Hospital.* She was essentially asymptomatic in bed. She gave no history of any allergic manifestations or of any worm infection. Repeated sputum examinations were negative for acid fast organisms. The urine remained negative. Her stools were negative for ova and parasites. Her blood picture is revealed in table 2.

TABLE II  
Summary of Data

Date	Tempera- ture F.	White Cell Count	Neutro- philes %	Differential Count		Eosino- philes %	Sedimenta- tion Rate mm. per hour
				Lympho- cytes %	Mono- cytes %		
6/11/45	100.2°	14,900	32	23	3	42	28
6/19/45	99.6°	14,700	42	21	2	35	
6/26/45	98.4°	9,450	42	32	2	24	
7/ 3/45	98.8°	11,000	57	29	5	9	10

A biopsy of the gastrocnemius muscle was done with regard to the possible presence of trichinosis or periarteritis nodosa. This was reported as negative. No significant pathologic changes were seen in the blood vessels. There was no significant leukocytic infiltration. This patient continued to improve subjectively. Formerly she would cough on deep breathing for examination but this ceased. Temperature, which had remained slightly elevated, spiking to 100.6° F. daily, gradually came down on the twelfth hospital day and remained normal after the sixteenth hospital day.

On the seventeenth hospital day a chest film (figure 5) showed the small areas of density previously noted in the lateral portion of the lower right lung field to have practically disappeared, and there were now only dense perivascular markings. On the left side, the patchy density in the middle third of the lung had largely disappeared. There was still some fine mottling. The basal third of the lung was hazier than before and showed some slight mottling with thickened markings suggesting a development in this area of a pneumonitis not present before. On the twentieth hospital day a reexamination of the chest including the examination of the esophagus with opaque mixtures showed no compression or alteration in the position of the esophagus. The areas of density in the right lung and left mid-lung field had largely disappeared, but there was still an area of increased density at the left base which represented an extension of the process. The hilar shadow and perivascular markings were accentuated on both sides and there was a dense sharply demarcated shadow just above the right hilum with a convex outer border which was consistent with an enlarged peritracheal lymph node. There was no evidence of free effusion in the pleural cavities.

On the twenty-fourth hospital day the patient was greatly improved and had practically no irritation in her trachea on breathing. She was up and about and climbing stairs. The eosinophilia was subsiding and her temperature was essentially normal. There were no signs in her chest on physical examination.

On the twenty-sixth hospital day chest reexamination, in comparison with the film of June 29, 1946, revealed the right lung field was now clear with no signs of parenchymal disease. On the left side the dense area previously seen at the base largely absorbed. The left diaphragm was now seen fairly distinctly. An electrocardiogram taken on the patient showed, except for somewhat low voltage through-

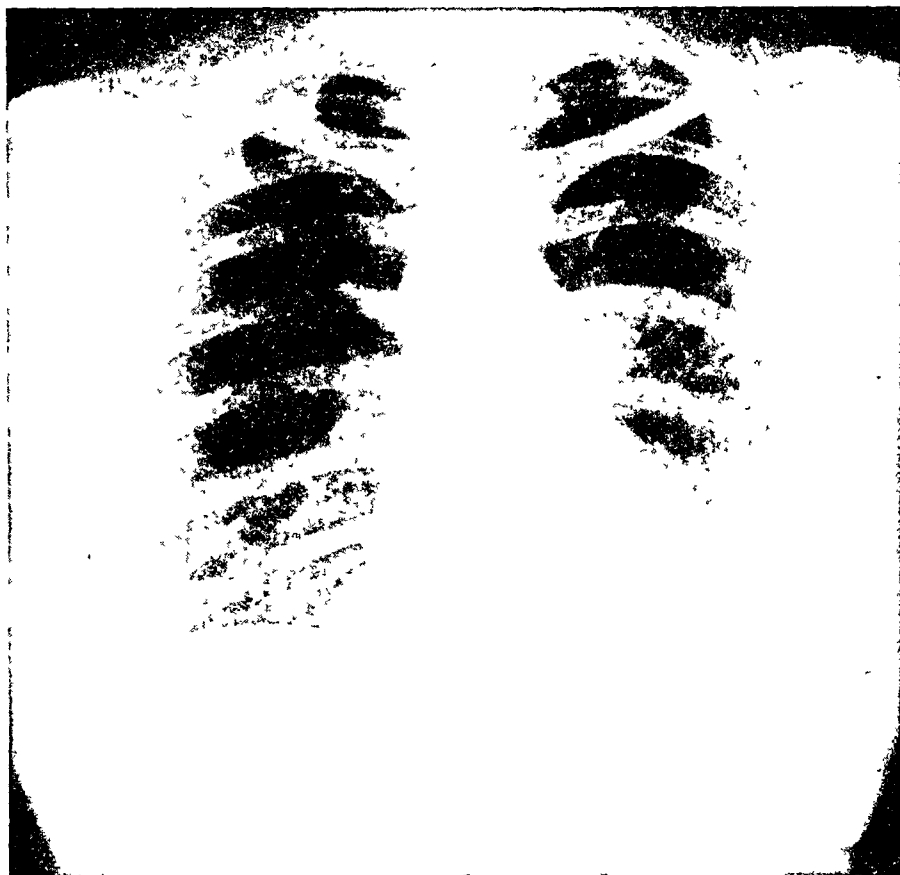


FIG. 5. Chest x-ray in Case 2 on seventeenth hospital day. It showed the patchy density of the middle third of the left lung to have largely disappeared. The left basal third of the lung was hazier than before suggesting a development of pneumonitis not present previously.

out, a normal record. The patient was discharged on the thirty-first hospital day as improved.

*Case 3.* H. S., a 27 year old white male veteran, was admitted to the hospital for the first time September 23, 1946 with the chief complaint of a chronic, slightly productive cough. The patient was well in all respects until August 1945, when in Paris, France, he contracted a cold from which was derived a chronic hacking, at times productive cough. The next month, September, he was separated from the service and returned to his home in Texas. However, the chronic cough persisted sometimes better and sometimes worse. For the next 11 months until August 1946,



it became associated with sharp pains in his right chest and periodic fever. The cough was productive of a moderate amount of greenish, mucoid phlegm, never associated with hemoptysis. On September 21, 1946 he was seen by his family physician and a chest roentgenogram revealed some infiltration in the right lung. Hospitalization was advised.

*Past History.* Except for his Army service the patient had lived on farms. He had never worked in mines or quarries. As a child he had had the usual diseases,



FIG. 6. Chest roentgenogram in Case 3 on September 23. It revealed almost complete consolidation of the right upper lobe.

all mild. Since the age of 18 years, he had suffered periodic attacks of hay fever when subjected to dust from corn and cornshucks. No other type of dust or allergies seemed to precipitate the hay fever. He had no history of asthma, migraine or urticaria. His battle service took him through North Africa, Sicily, Italy, Southern France, Austria and Germany. In 1942, while overseas, he was treated for acute gonorrhea with sulfadiazine with no residuals. He enjoyed excellent health until the last two months of his service.

*Family History.* The patient's father and one brother had had moderately severe asthma for many years. A sister suffered from moderate hay fever. There was no history of familial tuberculosis or known contacts.

*Review of Systems.* Non-contributory.

Physical examination was essentially negative at this time except for hypertrophied tonsils. Initial laboratory studies showed a normal urinalysis. Blood count revealed 11,000 white blood cells, 62 per cent neutrophils, 22 per cent lympho-

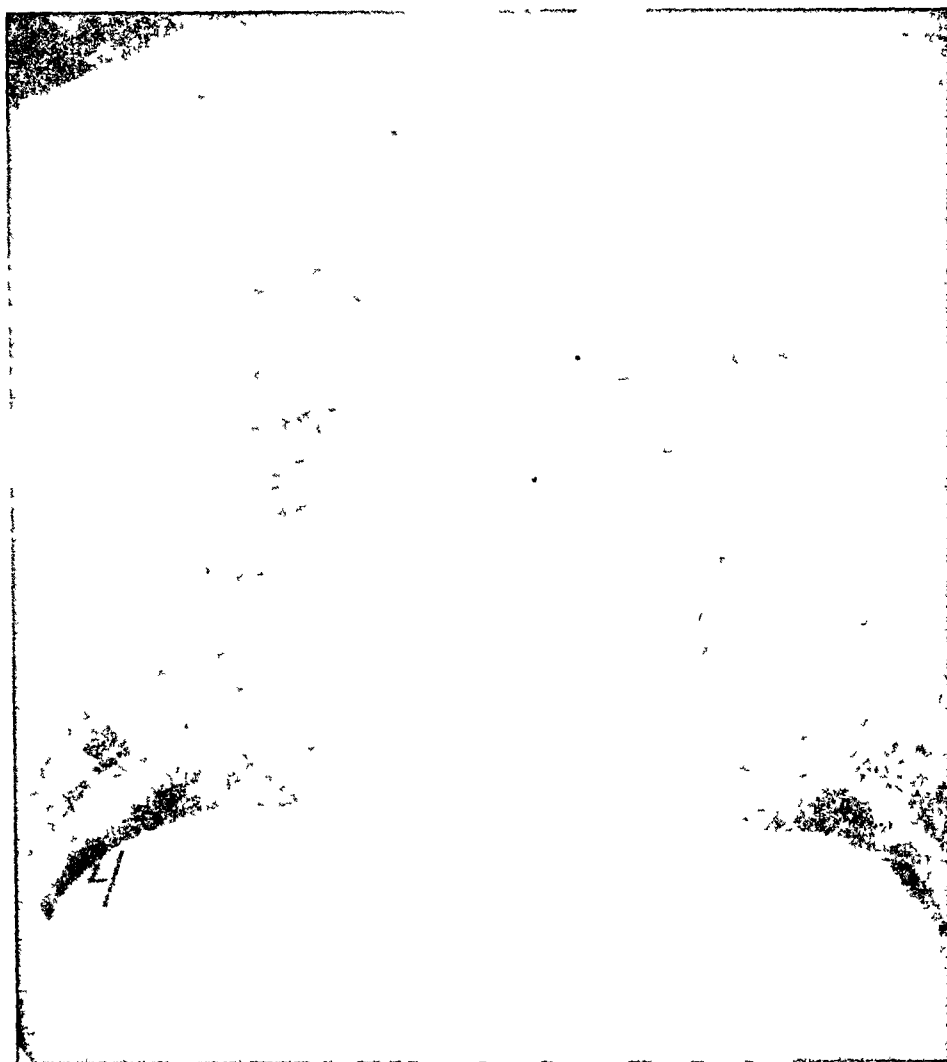


FIG. 7. Chest roentgenogram in Case 3 on October 7. It showed considerable resolution of previously described infiltration in the right upper lung field.

cytes, 15 per cent eosinophiles, 1 per cent basophiles, hemoglobin 80 per cent; sedimentation rate (Westergren) 51 mm. in one hour. He was observed particularly for pulmonary tuberculosis, but repeated sputum examinations were negative for acid fast organisms. Chest roentgenograms were reported as follows: September 23 (figure 6). "Except for several small rounded areas of rarefaction there is almost complete consolidation of the right upper lobe. The lung fields are otherwise essentially clear." September 25. "There is a large area of infiltration involving the

posterior segment of the right upper lobe, limited by the interlobar fissure between the upper and middle lobe. Within this area of infiltration several small translucencies are seen. The remaining lung fields are clear." October 2 (figure 7). "Reëxamination of the chest shows considerable resolution of the previously described infiltration in the right upper lung field. There is now only a small triangular area of infiltration in the periphery of the first costal interspace anteriorly. There is a small area of fibrosis in the second left costal interspace anteriorly extending from the hilum toward the periphery." October 7, 1946. "Reëxamination of the chest shows further resolution of the previously described infiltration in the right upper lobe posteriorly." October 21. "There is a slight increase in the amount of clearing over the previous examination. There is still a small zone of fibrosis at the level of the second rib anteriorly." October 31. "There is complete clearance of the previously described infiltration in the right upper lobe. No evidence of pulmonary tuberculosis." The patient was observed for 44 days and discharged with a diagnosis of resolved pneumonia. He was apparently well on November 6, 1946.

Second Hospital Admission (December 17, 1946).

The patient was admitted to the ENT Service for a tonsillectomy. After his last discharge he had felt well for a while but then began to have frequent sore throats and fever. A routine chest roentgenogram (figure 8) was taken and this was reported as "showing a fairly large area of consolidation in the second and third left costal interspaces anteriorly near the periphery. There is also infiltration in the left lower lung field near the left cardiac border. The right lung is clear." Tonsillectomy was postponed and the patient was transferred to a medical ward. At this time his only complaints were chronic cough, productive of small amounts of tenacious, mucoid sputum, and chest pains in the right mid-chest and lower left chest, described as sharp, catchy-like, related to respirations.

Physical examination at this time showed only hypertrophied tonsils. At times during his hospital stay occasional râles were heard in the left upper lung field without change in fremitus or resonance. His temperature remained normal except for three episodes of low grade fever. Initial laboratory studies showed a red blood cell count of 4,460,000, hemoglobin 90 per cent; white blood cells, 19,900 with 59 per cent neutrophils, 11 per cent eosinophiles, 25 per cent lymphocytes, 5 per cent monocytes (table 3). On following examinations, the eosinophilia was reported as 29 per cent,

TABLE III  
Summary of Data

Date	Temperature F.	White Cell Count	Neutrophils %	Differential Count		Eosinophiles %	Sedimentation Rate mm. per hour
				Lymphocytes %	Monocytes %		
9/23/46	99.6°	11,000	62	22	1	15	51
12/18/46	98.6°	11,900	59	25	5	11	
1/ 2/47	99.2°	9,600	38	29		33	20
1/ 6/47	99.0°	8,300	38	40		22	
1/ 8/47	99.0°	11,000	38	20		42	
1/ 9/47	98.6°	8,000	26	39		35	
1/15/47	99.8°	8,200	40	30	2	28	10
2/ 3/47	98.6°	10,250	55	35	1	9	

22 per cent, 42 per cent, 35 per cent, 28 per cent, 9 per cent. Other blood studies were normal. Repeated urinalyses were negative. Sputum cultures and smears for acid-fast organisms were negative. Smears showed numerous eosinophiles. The feces were negative for ova and parasites. Tuberculin skin test was negative, as

were skin tests for trichinosis and coccidioidomycosis. Roentgen-ray reports (December 30, 1946). "There has been marked clearing of the consolidation in the left upper lung field. The infiltration in the lower lung fields is still demonstrable and the right upper lobe shows a residual increase in the pulmonary markings." January 6, 1947. "The left lung field is now essentially clear. There is a recurrent area of infiltration in the inner zone of the first right costal interspace anteriorly consistent with recent pneumonitis." January 14, 1947. "There is a small residual area of



FIG. 8. Chest roentgenogram in Case 3 on second admission, December 17. It showed a fairly large area of consolidation in the second and third left costal interspaces anteriorly near the periphery. There was also infiltration in the left lower lung field near the left cardiac border. The right lung was clear.

infiltration in the right subapical region near the inner zone and another fairly round area of infiltration in the right lower lung field." February 14, 1947. "Reëxamination of the chest shows both lung fields to be clear except for a linear area of increased density in the inner zone of the right apical region." The common agglutination tests were all normal. On February 10 the patient underwent an uneventful tonsillectomy and was discharged as improved February 20. After his discharge he remained free from symptoms except for mild hacking cough.

## DISCUSSION

Case 1 presented a very unusual clinical course, and review of the literature has not revealed any similar case report. The onset of illness, on her first admission, was rather sudden, with physical findings minimal compared to the roentgenographic findings. She became very ill but her clinical picture did not resemble that of a true infectious pneumonia. Her skin was cool and moist. She had an expiratory grunt and tachypnea with short shallow respirations. Her white count rose as high as 31,950 with an eosinophilia of 41 per cent. The course was unusually stormy and she showed no response to sulfonamide therapy. It is interesting to note that on April 14 she received intravenous aminophylline and her pulse, temperature and respirations were within normal limits again for a few days. She developed a dry, hacking, non-productive cough, and her periods of intense cyanosis and apnea responded dramatically to intravenous aminophylline. Her blood, urine, and sputum cultures were consistently reported sterile. The stools were negative for ova and parasites. A skin test for trichinosis was negative. She had no previous allergic history but both her brother and sister gave a history of seasonal hay fever. On discharge her chest plate was clear and repeated check-up showed no recurrences of infiltration.

On her third admission, 18 months later, she developed a picture of tracheobronchitis. Again her chest and roentgenograms showed changing areas of density. She showed no response to penicillin therapy. Her highest eosinophilia was 4 per cent during this admission. It was the opinion of the roentgenologist that roentgenographic findings on the first admission resembled an interstitial pneumonitis, whereas on her third admission they were more consistent with an atypical pneumonia. This corresponded with her clinical picture.

The second patient ran a more benign course. She developed an irritating cough and ran a slight fever of 100 to 101.2° F. for 17 days. The chest never revealed any abnormal physical findings but roentgenograms showed changing shadows. Her eosinophilia reached 42 per cent. All tests for acid fast infection, ova and parasites, allergens, trichinosis, and periarteritis nodosa were negative. We felt that her symptomatology was too severe and the duration of her illness too great to represent a true Loeffler's syndrome. It is interesting to note that her onset resembled angina pectoris.

Our third case had a rather prolonged course with two episodes of pulmonary infiltration and eosinophilia. This patient had a positive family history for allergy and he himself had hay fever. Unfortunately skin tests were not done. All other tests were again negative as in first two patients.

As has been mentioned, the cause for this syndrome is not known, although hypersensitivity is suspected from its frequent association with vasomotor rhinitis and asthma. Various substances have been considered allergens in causing pulmonary infiltrations with eosinophilia.

Miller et al.<sup>9</sup> reported on a syndrome which they called allergic bronchopneumonia. Eleven cases were presented, most of whom had a positive allergic history. In describing the clinical picture they define it as a pneumonia or bronchial process in an allergic individual characterized by signs and symptoms indicative of bronchial obstruction and pulmonary infiltration with or without fever. The etiology or the predisposing cause is an underlying allergic constitution. Unlike true infectious pneumonia, the skin is usually cold and moist and pleuritic pain is conspicuous by its absence. The degree of cyanosis is variable. Examination of the nose shows boggy, purplish-white mucous membrane, and smears of nasal secretions will reveal numerous eosinophiles. The course may be shortened by administration of epinephrine which may produce a sudden cessation of symptoms and initial drop in temperature. Complications are rare. Death occurred in only one case. The causes mentioned were allergic shock, extensive allergic pneumonia, massive atelectasis or spontaneous pneumothorax.

Engel<sup>10</sup> described a similar clinical picture of pulmonary infiltration and blood eosinophilia in himself and a friend, and attributed the condition to hypersensitivity to the pollen of the privet plant. He considered bronchial asthma, atelectasis and traumatic origin, but found no confirmatory evidence.

Smith<sup>6</sup> presented a case of pulmonary infiltration with eosinophilia of 69 per cent in a 55 year old patient with previous history of severe bronchitis and asthma. Roentgenographic findings persisted from June 6 to July 18.

Baer<sup>11</sup> reported another case in a 30 year old asthmatic with lung infiltration and eosinophilia of 25 per cent. The infiltration shown by roentgen-ray was present from December 27 to January 6.

Karan and Singer<sup>12</sup> reported five cases of extensive pulmonary infiltration which roentgenographically simulated pneumonic tuberculosis. In two of these cases, there was eosinophilia of 9 and 15-per cent respectively. One had had attacks suggestive of mild asthma for many years; the other had an attack, during the course of illness, which was diagnosed as asthma by the referring physician. They were treated with adrenalin with some relief. The authors compared these cases to Loeffler's syndrome but stated that they differed in some respects from this condition, e.g., the symptoms were more persistent and pronounced, pulmonary infiltration was less rapid in clearing, and in one there was evidence of cardiac strain which subsided when the pulmonic condition subsided. It appears to us that when these two cases are compared with their other three and reported cases of atypical pneumonia of unknown etiology, so-called virus pneumonia, there are marked similarities. Differential points are eosinophilia and evidence suggestive of asthma. This suggests that these are instances of similar diseases occurring in allergic individuals. Whether the disease occurring in an hypersensitive individual merely stimulates the production of the eosinophiles on a non-specific basis, or whether the individual actually becomes hypersensitive to his new infection must be left to speculation. The condition occurs frequently enough

without asthmatic or other usual hypersensitive manifestations to warrant the consideration of the latter cause of eosinophilia.

Weingarten<sup>13</sup> described a disease entity peculiar to India beginning with lassitude, fever of 100 to 101° F. in the evening, loss of weight, development of a dry, hacking cough, and development in about a week of expiratory dyspnea lasting several weeks. It was often accompanied by considerable wheezing and some cases had severe attacks of typical bronchial asthma occurring regularly at night. Physical signs included sibilant and sonorous rhonchi and prolonged respirations. Sputum was absent or scarce, tenacious and glassy. Splenomegaly three to five centimeters below the costal margin was present. The eosinophilia was striking, going as high as 88 per cent. Roentgenographic examination showed nonconfluent disseminated mottling of both lungs.

Peirce and his associates<sup>14</sup> described several cases with blood eosinophilia and focal pulmonary edema. Six of the eight cases had definite history of asthma or some specific hypersensitivity. The authors believed that the roentgenographic evidence strongly suggested that this variation from the normal was probably due to interstitial edema rather than to the cellular infiltrate of an infection. Consideration of "transient focal pulmonary edema" was suggested as the probable pathophysiologic process, perhaps as one of the manifestations of allergy.

In 1944 Peabody,<sup>15</sup> in citing the paucity of cases in the American literature, said: "My own search of the American and English literature has revealed considerably fewer than 25 cases, even if all reported cases should be accepted as authentic." He reported a patient who had chronic "asthma" and who was hospitalized three times with asthmatic attacks, fever, pulmonary involvement and high eosinophilia. On one occasion the entire left lung field was occupied by an extensive infiltrative process and possible cavity. Four months later the lung fields were clear. We feel that this patient's manifestations were too severe for a true Loeffler's syndrome.

In 1933 Cole and Korns<sup>16</sup> recorded an instance of recurrent pulmonary involvement associated with angioneurotic edema and high eosinophilia. Serra<sup>17</sup> mentioned that except for the fact that this patient died the case had some resemblance to the syndrome.

Bagenstoss and his associates<sup>18</sup> reported a case in a woman aged 59 with "symptomatic nonspasmodic 'asthma' of seven years' duration." She complained of severe cough, breathlessness and anorexia. Roentgenograms of the chest showed infiltrations which apparently lasted from June 24, 1944 to her discharge September 11, 1944. On December 31 she suddenly became ill with substernal discomfort and severe, progressive dyspnea and died five days later. At autopsy there were large numbers of eosinophiles in the pneumonic exudate and granulomatous and fibrous changes with necrotic arteritis and phlebitis of the allergic type. The authors present this as a case showing the outstanding histological features of pulmonary lesions in

a case of Loeffler's syndrome. They suggested also that the picture appeared quite similar to the changes observed in periarteritis nodosa.

Müller,<sup>19</sup> also quoted by Schultze,<sup>20</sup> considered that the pulmonary infiltrations associated with eosinophilia and described by Loeffler were a result of ascaris infiltration although the ascaris frequently were not demonstrable in the sputum or in the stools. He cited as evidence the following occurrences. In January and February of 1938, four physicians including himself developed the typical clinical picture after the repeated eating of young cress that had been grown in a greenhouse. It had been fertilized by manure from pig and horse stables. Ascaris larvae could not be demonstrated in the sputum at the time nor could young worms be found in the stools later. As final proof of the causes of these cases he took by mouth three teaspoonfuls of the soil in question. After the expected incubation period of eight days, the typical symptoms complex developed and lasted the usual length of time, with multiple shifting lung infiltrations, mild degree of illness, eosinophilia up to 19 per cent, and leukocytosis. Unfortunately no mention was made of any attempt to recover ascaris forms from the soil ingested.

Loeffler<sup>2</sup> cites the work of Koino<sup>21</sup> who showed ascaris eggs in the stool either before, during or after the onset of the pulmonary infiltration. Koino showed that ascaris larvae in their wandering can cause pneumonia—highly febrile, clinically severe with hemorrhagic sputum in which from five to 10 days ascaris larvae in great numbers can be demonstrated. This was experimental, Koino having swallowed 2000 ripe fertilized eggs.

Other parasites and ova have been associated with eosinophilia and pulmonary infiltration. Stephano<sup>22</sup> reported a case that had amebae in the sputum but not in the stool, and both the lung infiltration and accompanying asthma disappeared after emetine therapy.

Hoff and Hicks<sup>5</sup> reported one case in which symptoms and roentgenographic findings persisted for four months until amebae were eliminated from the stool. The patient showed dramatic response to emetine therapy. Lavier, Bariety and Caroli<sup>23</sup> have reported this syndrome in a case of infestation with *Fasciola hepatica*. Miller<sup>4</sup> reported a case with a maximum of 85 per cent eosinophilia. Ova of *Trichuris trichiura* were found in the stools. These disappeared on antihelminthic treatment but the clinical course was unaffected. The patient also received mapharsen therapy and improved.

Wright and Gold<sup>24</sup> observed nine cases of cutaneous helminthiasis with associated pulmonary infiltrations and peripheral eosinophilia. The authors stated that "When erroneous diagnosis or procrastination in therapy of the local skin lesions occurred, the pulmonary infiltrations continued a migratory course over a period of weeks."

Scherlis<sup>25</sup> presented one case with a benign course with roentgenographic findings on November 19 and November 23, which had cleared by November 27. Jones and Souders<sup>7</sup> reported a case in a 33 year old negress in whom



the illness was mild. Roentgenographic findings in the chest were present from October 21, with complete disappearance by December 7.

In 1939 Smith and Alexander<sup>28</sup> presented a fatal case of so-called "Loeffler's syndrome" in a seven year old girl. The girl had bronchopneumonia in September with a relapse in October. Examination showed malnutrition, bronchitis, anemia, white blood count 31,000 with 39 per cent eosinophilia, a spiking temperature to 104.5° F., bilateral transient miliary infiltration; the peak eosinophilia at 10 days was 54 per cent. She had a long stormy course. Postmortem examination showed hemorrhagic and necrotic areas in the lungs. Although leukemia seemed likely, no definite diagnosis was made. The whole picture did not fit a true Loeffler's syndrome.

Serra<sup>17</sup> presented a case in which there were four separate attacks over a period of 32 months. The fourth attack was of 26 months' duration at the time of the article's appearance. The etiologic factor could not be determined but the occurrence of hives, eczema and eosinophilia supported hypersensitivity as a basic factor.

In 1942 Elsom and Ingelfinger<sup>27</sup> reported two cases of pulmonary infiltration accompanied by an eosinophilia and definite evidence of brucellosis in both cases.

Coccidioidomycosis must also be considered, since it is primarily and predominantly a pulmonary disease and is associated with various roentgenographic findings and eosinophilia up to 89 per cent.<sup>28, 29, 30</sup>

#### COMMENT

Since Loeffler's original article,<sup>1</sup> there has been much written and said about Loeffler's syndrome. With the present tendency to pigeon-hole every disease under a definite name, a great many conditions with superficial resemblance to Loeffler's syndrome have come to be described under that name. This seems rather unfortunate in that it tends to cloud the matter in a veil of uncertainty and to imply that it is a disease with varied clinical manifestations and definite etiology, rather than a restricted symptom complex of unknown and possibly varied etiology. Loeffler's syndrome is a distinct entity characterized by migratory and at times recurrent benign pulmonary infiltrations.

Müller<sup>19</sup> has given the most suggestive evidence that there may be a specific organism that causes the symptom complex, although he was unable to demonstrate the organism, nor did he give any evidence that different organisms might not produce the same effect.

Most of the other cases of pulmonary infiltration with eosinophilia that we have found in the literature in this country do not conform strictly to the syndrome described by Loeffler. It seems possible that they may be variants of the same pathological process which is produced by the same or by somewhat similar etiological agents, such as parasitic worms. With few exceptions, notable in the cases of Jones and Souders,<sup>7</sup> Baer,<sup>11</sup> and Scherlis,<sup>25</sup> the

illness was too severe or the signs of too long duration to warrant, it seems to us, labelling them Loeffler's syndrome.

Serra<sup>17</sup> mentioned that this disease is reported under many different titles with Loeffler's syndrome added in parentheses. He suggested the term "Benign pulmonary infiltrate" to allow for the inclusion of possible cases without eosinophilia, as well as those of longer duration than usual. We feel that the cases which fit into the initial symptom complex should be called Loeffler's syndrome but suggest that all other cases be termed pulmonary infiltration with blood eosinophilia associated with an unknown or known etiological factor.

In general, there has been a tendency to associate with Loeffler's syndrome any case with pulmonary infiltration and eosinophilia. This combination of pulmonary infiltration and eosinophilia may appear in any age group, from infancy to old age. It may be associated with a benign and mild clinical picture, as in true Loeffler's syndrome, but in some cases the course has been very stormy, as illustrated by Smith and Alexander's case and by our first case, whereas our second and third cases showed a less severe, but quite protracted course. It has occurred in association with definite asthmatic tendencies or other specific allergies, with *Endameba histolytica* infection and other parasites such as *Fasciola hepatica*, *Ascaris lumbricoides*, and trichinosis,<sup>31</sup> with cutaneous helminthiasis and with brucellosis. In many cases no specific etiological factor or agent has been demonstrated. It is an unusual response of the body tissues which is occasionally seen in many different conditions, with or without the manifestations generally considered to be hypersensitive in nature.

Search for the etiological agent is important in each case. In one instance, there may be a specific allergen to which the patient is sensitive or there may be a parasitic infestation which will respond to specific therapy. These may be found only by thorough study of the history, clinical findings, and laboratory investigations. As Miller<sup>4</sup> pointed out, periarteritis nodosa, Hodgkin's disease, and eosinophilic leukemia must be considered in the differential diagnosis, but usually can be ruled out by the clinical course. Familial eosinophilia could not be ruled out in his case. Pulmonary tuberculosis must be considered, and the patient followed carefully.

In case of an allergic background or a stormy course, it must be borne in mind that adrenalin or aminophylline may alleviate the course. In our first case, it appeared that the patient would have died had it not been for the administration of aminophylline intravenously. Miller and his associates<sup>9</sup> found epinephrine useful in their reported cases of allergic bronchopneumonia.

## SUMMARY

1. Three cases of pulmonary infiltration with blood eosinophilia are reported.

2. The first case had a long, stormy course which did not resemble the typical Loeffler's syndrome. The second case had a less severe but quite protracted course with onset suggesting angina pectoris. The third had a prolonged course with two episodes, and of the three cases it was the only one with a definite hypersensitive background.

3. In none of the cases was an etiological agent found.

4. Various conditions in which pulmonary infiltration and blood eosinophilia are associated have been reviewed.

5. The importance of searching for an etiological agent and giving specific therapy when indicated is emphasized.

6. A plea for a more useful and standard nomenclature is made.

### BIBLIOGRAPHY

1. LOEFFLER, W.: Zur differential Diagnose der Lungeninfiltrierungen über flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk., 1932, lxxix, 368-382.
2. FREUND, R., and SAMUELSON, S.: Transitory infiltration of lung with eosinophilia: Loeffler's syndrome, Arch. Int. Med., 1940, lxvi, 1215-1220.
3. LOEFFLER, W.: Die flüchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr., 1936, lxvi, 1069-1078.
4. MILLER, H.: Transitory lung infiltrations accompanied by eosinophilia. Report of a case, New Eng. Jr. Med., 1945, ccxxxii, 7-10.
5. HOFF, A., and HICKS, H. M.: Transient pulmonary infiltrations: case with eosinophilia (Loeffler's syndrome) associated with amoebiasis, Am. Rev. Tuberc., 1942, xlv, 194-199.
6. SMITH, J. H.: Loeffler's syndrome, South. Med. Jr., 1943, xxxvi, 269-271.
7. JONES, S. H., and SOUDERS, C. R.: Eosinophilic infiltration of lungs, New Eng. Jr. Med., 1944, ccxxxix, 356-358.
8. Editorial: The allergic pulmonary reactions of Loeffler's syndrome, Jr. Am. Med. Assoc., 1947, cxxxiii, 325.
9. MILLER, H., PINESS, G., FEINGOLD, B. F., and FRIEDMAN, T. B.: Allergic bronchopneumonia, Jr. Pediat., 1935, vii, 768-790.
10. ENGEL, D.: Über eine Eigenartige Anaphylaktische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk., 1935, lxxxvii, 239-250.
11. BAER, A.: Report of a case of transient pulmonary edema (Loeffler's syndrome), Ohio State Med. Jr., 1941, xxxvii, 960-961.
12. KARAN, A. A., and SINGER, E.: Transitory pulmonary infiltrations mistaken for tuberculosis: with report of five cases, Ann. Int. Med., 1942, xvii, 106-124.
13. WEINGARTEN, R. J.: Tropical eosinophilia, Lancet, 1943, i, 103-105.
14. PEIRCE, C. B., CRUTCHLOW, E. F., HENDERSON, A. T., and MCKAY, J. W.: Transient focal pulmonary edema, Am. Rev. Tuberc., 1945, xii, 1-14.
15. PEABODY, J. W.: Transitory migratory pulmonary infiltrations associated with eosinophilia (Loeffler's syndrome), Dis. Chest, 1944, x, 391.
16. COLE, J., and KORNS, H. M.: Visceral manifestations of angioneurotic edema, Jr. Allergy, 1933, v, 347.
17. SERRA, L. M.: Loeffler's syndrome, Bull. School Med., Univ. Maryland, 1945, xxx, 11-31.
18. BAGENSTOSS, A. H., BOYLEY, E. C., and LINDBERG, D. O. N.: Loeffler's syndrome: report of a case with pathologic examination of the lung, Proc. Staff Meet., Mayo Clin., 1946, xxi, 457.

19. MÜLLER, R. W.: Zur Pathogenese der flüchtigen Eosinophilie Lungeninfiltrate, *Deutsch. med. Wchnschr.*, 1938, lxiv, 1286.
20. SCHULTZE, H.: Zur Frage der flüchtigen Eosinophilen Lungeninfiltrierungen, *Beitr. z. Klin. d. Tuberk.*, 1940, xcv, 1.
21. KOINO, S.: *Japan Med. World*, 1922, ii, 11 (cited by Loeffler, 1936).
22. STEPHANO, J.: Syndrome asmatico por Amoebiasis Pulmonar, *Semana méd.*, 1939, xlv, 749.
23. LAVIER, G., BARIETY, M., and CAROLI, J.: Distomatose hepatique et syndrome de Loeffler, *Paris méd.*, 1939, i, 434-439.
24. WRIGHT, D. O., and GOLD, E. M.: Loeffler's syndrome associated with creeping eruption (cutaneous helminthiasis), *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1082.
25. SCHERLIS, S.: Loeffler's syndrome—eosinophilic pneumonia, *Mil. Surg.*, 1945, xcvi, 349-354.
26. SMITH, D. C. W., and ALEXANDER, A. J.: Transitory lung infiltrations associated with eosinophilia, *South. Med. Jr.*, 1939, xxxii, 267-273.
27. ELSOM, K. A., and INGELFINGER, F. J.: Eosinophilia and pneumonitis in chronic brucellosis: report of 2 cases, *Ann. Int. Med.*, 1942, xvi, 995-1002.
28. DAVIS, B. L., Jr., SMITH, R. T., and SMITH, C. E.: Epidemic coccidioidomycosis, *Jr. Am. Med. Assoc.*, 1942, cxviii, 1182-1186.
29. DICKENS, E. C.: Coccidioidomycosis, *Jr. Am. Med. Assoc.*, 1938, cxi, 1362-1365.
30. WILLET, F. M., and OPPENHEIM, E.: Pulmonary infiltrations with associated eosinophilia, *Am. Jr. Med. Sci.*, 1942, ccxii, 608.
31. MINOT, G. R., and RACKEMANN, F. M.: Respiratory signs and symptoms in trichinosis, *Am. Jr. Med. Sci.*, 1915, cl, 571.

# OBESITY AND ITS TREATMENT, WITH PARTICULAR REFERENCE TO THE USE OF ANOREXIGENIC COMPOUNDS\*

By ROBERT H. WILLIAMS,† M.D., F.A.C.P., *Boston, Massachusetts*, WILLIAM H. DAUGHADAY, M.D., *St. Louis, Missouri*, WALTER F. ROGERS, JR., M.D., *Boston, Massachusetts*, SAMUEL P. ASPER, JR., M.D., *Baltimore, Maryland*, and BEVERLY T. TOWERY, M.D., *Boston, Massachusetts*

IN spite of the frequent enlightening discussions in social and scientific circles on factors contributing to the development of obesity and on the treatment of this condition, there continues to be a vast number of markedly obese individuals. The deleterious effects produced by this condition, directly or indirectly, are much greater than seems to be generally recognized. In addition to the social and occupational handicaps and associated mental distress which obesity causes, it predisposes to the development of cardiovascular diseases and diabetes mellitus. Marked obesity exerts a pronounced effect on life expectancy. For example, Dublin and Lotka<sup>1</sup> found that individuals aged 45 to 50 with excess weight of 50 pounds had a 56 per cent increase in death rate, and the ones with an excess of 90 pounds had a 116 per cent increase.

For several years we have followed a number of obese patients in the Endocrine Clinic of the Boston City Hospital. In treating these individuals we explained the disease to the patient as being one of a positive calorie balance and we attempted to point out certain factors which modified this balance. We endeavored to treat the obesity chiefly by restricting the food intake to from 400 to 1200 calories per day and by correcting some of the factors which contributed to the obesity. Occasionally desiccated thyroid was used as an adjunctive therapy, and more often "Benzedrine" was prescribed. This regimen proved to be satisfactory in many patients, but many others were seen from year to year in more or less the same markedly obese state, in spite of the many prolonged "sermons" which had been "preached." These failures in therapy were due largely to the patient's inadequate will-power to execute the prescribed regimen. Consequently, we chose to decrease the desire for food by administering anorexigenic compounds of a type similar to "Benzedrine." The latter drug had proved to be unsatisfactory in many patients because of certain undesirable symptoms which it produced. Therefore, several compounds were studied in the hope of ob-

\* Received for publication November 18, 1947.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

† Now at Department of Medicine, University of Washington, Seattle, Washington.

taining ones which had pronounced anorexigenic effects without other undesirable actions.

Before describing the studies with these drugs, factors contributing to obesity are discussed because drug therapy should be considered only as an adjunctive therapeutic measure. As will be indicated later, the chief effect of the compounds used was to decrease the total amount of food ingested. In cases where an adequate restriction of food intake can be voluntarily induced, there is no need to prescribe the anorexigenic compounds. Moreover, it is important to correct as many of the factors contributing to obesity as possible, whether or not specific drug therapy is given.

### CONSIDERATION OF FACTORS CONTRIBUTING TO OBESITY

A lengthy discussion of the factors considered by various investigators as contributing to obesity is not given in this paper, since there have been many reviews on the subject, among which may be mentioned those by Newburgh<sup>2</sup> and Evans.<sup>3</sup> Many of the comments which we make are not original, but seem to warrant repetition because of the frequent use of unsatisfactory therapy in obesity.

It is clear that obesity results from the ingestion of more food than is utilized. However, there are a vast number of factors which may influence this balance and it is often advisable to attempt to correct them as much as possible. We like to obtain the patient's opinion as to the cause of his obesity. Although his ideas may be inaccurate, they often afford the basis for peculiar behavior, dietary or otherwise.

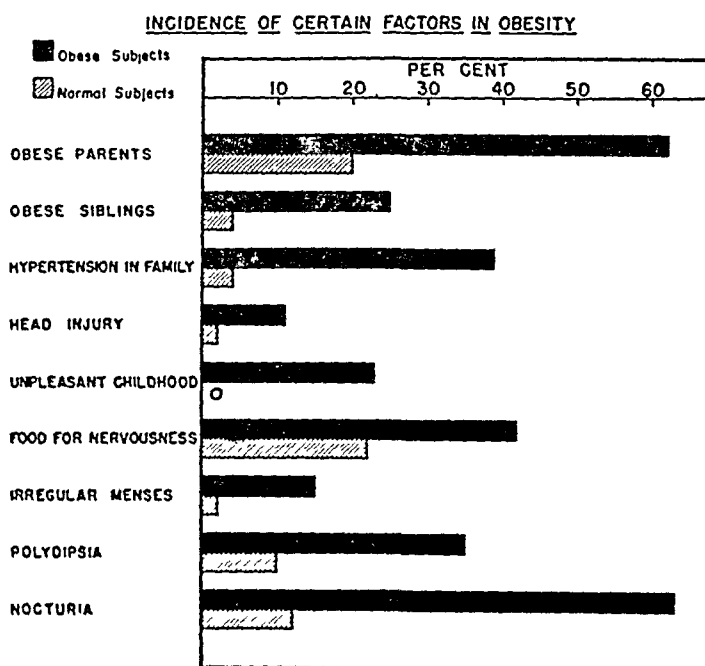


FIG. 1.

Ninety-six markedly obese subjects, chiefly nurses, were studied carefully with reference to their family background, environment, development, general eating habits and physical status. For comparison, 50 non-obese individuals were selected with reference to occupation, social and economic status, age and sex. The tabulations of the observations in these groups of individuals are in accord with the conclusions drawn from experience with much larger series of patients followed in this clinic.

Only 12 per cent of the patients were of the impression that "glandular disease" was primarily responsible for their obesity. Seventy-eight per cent stated that overeating had caused their excess weight and listed a variety of factors, discussed later, which contributed to this. The other 10 per cent admitted that they did not have a good concept of the factors causing obesity.

1. *Family Influences.* As may be observed in figure 1, obesity occurred much more frequently among the parents and siblings of obese patients than of normal individuals. Wilder<sup>4</sup> suggested that in some instances of familial obesity there might be an increased activity of the centers of the diencephalon controlling feelings of hunger and satiety. The exposure to the same environment and habits is doubtless important in family obesity. Twenty-three per cent of the patients, compared with 12 per cent of the controls, stated that their family tended to eat excessively. In some families the caloric requirements of certain members were much higher than for others, but the same bountiful servings were given for each, and the child was punished if he did not "clean the plate."

TABLE I  
Age at Which Patient Considers That He First Became Definitely Obese

Years	Per Cent
0-10	16
10-20	21
20-30	27
30-40	27
40-49	9

As shown in table 1, only 37 per cent of the subjects considered that they were obese before the age of 20; however, in many instances it was the continuation of family habits of overeating which led to the development or increase of obesity.

2. *Emotional Influences.* Perhaps the most underrated cause of obesity is the soothing effect of eating upon certain emotional tensions as well as upon a general state of nervousness. Some patients stated that when they were restless, lonesome or bored they obtained some relief by eating. Others were so comforted during feelings of abuse, whether caused by episodes of disappointment or misfortunes in life, or physical defects. A feeling of unpopularity among friends and relatives was particularly conducive to hyperphagia. Sometimes this mechanism of compensation for maladjustments was instituted more by the parents than by the patient.

On the other hand, some patients in their desire "to be sociable" ate more food than they knew was required, as illustrated by the following comments made by a highly intelligent and well-informed patient. "It is impossible to diet and eat with normal individuals who are on regular diets. All social activities of life center around either eating or drinking and no one is really conscious of this until he or she gets on a diet; then there is a constant barrage of invitations to dinners, to tea, to cocktail parties, to go off for the week-end, or play bridge and be served refreshments—even to drink a Coca Cola, which has 80 calories. Often one ponders what more life could offer to a thin person than to a fat one, and the only answer is more years to enjoy it." In this patient is illustrated the important rôle of her philosophy upon her state of obesity. This individual is acquainted with most of the known pertinent facts about obesity and can choose her course. However, there are many individuals who eat excessively "to be sociable," but do not realize that marked obesity may result ultimately and may interfere greatly with their social standing and general happiness. It is perhaps the final realization of this situation that partly accounts for the higher incidence of suicides<sup>5</sup> in obese individuals than in non-obese ones. Fifty-one per cent of our patients stated that they were nervous or "high-strung." Many said that "inwardly" they were nervous.

The state of unhappiness often came on gradually over an interval of many years and was intensified as part of a vicious cycle that could be avoided. For example, Mrs. B., aged 46, and her husband were each slightly overweight at the time of their marriage 20 years previously. Mr. B. was very popular and his interest in civic activities frequently kept him away from home at night. Upon these occasions Mrs. B. usually attended a movie. She generally went alone since it was too troublesome to get someone to go with her. She would feel lonely when she got home because it was usually an hour or more before her husband arrived. During this time she ate various things "even though I was really not hungry, but because I received a reimbursement in food of what I lacked in other pleasures. It allayed some of my nervousness and gave me something to do." As the years passed and her weight increased greatly she found that the climb up the high hill from the movies to her home was strenuous exertion, so she began going home in a taxi-cab. Soon the pleasure derived from the movies did not seem to justify the expense involved so she just stayed at home and "nibbled at food." As her weight neared and passed 300 pounds she became ashamed to appear in public and felt that her husband was ashamed of her. Moreover, her husband's relatives were quite critical of her slovenly state. These factors made the patient feel all the more sorry for herself and more nervous; as a consequence she ate more. She finally became very high-strung and believed that there was nothing in life for her but misery. In treating this patient we not only helped her to lose more than 100 pounds, but assisted her in planning activities which would contribute to the betterment of her community and her family. She gained so much pleasure from



this type of work that she no longer had to depend upon eating for her pleasures.

The following statements made by one patient illustrate a not-uncommon problem in obesity. "Early in life I think that old-fashioned doctors, over-indulgent parents, etc., thought that a chubby baby was pretty and healthy, so nothing was done to control my diet. As I grew up, fat, awkward and bespectacled, I was too unhappy to do anything beyond feel sorry for myself. My sister was pretty and slim and I was jealous."

Another patient made these comments: "I believe that most people are obese because of improper eating habits. People who are obese eat, not, I am certain, from a need of food, but for the sensual pleasure derived from flavors which are pleasant to them. I, also, eat long after I am full because I enjoy food flavors. I consider this a form of infantile greed. Occasionally, I find myself restless enough so that I am unable to divert myself by reading, etc. At such times I usually eat."

The comments made by the aforementioned patients, as well as ones made by others, indicate that many of the patients had a good insight into some of their dietary troubles.

3. *Eating Habits.* Many patients related that they ate most of their food at night. They stated that they ate little or no breakfast and a light lunch, but ate a "good" evening meal and continued to eat "off and on" until bed time. Some of the patients had so little desire for breakfast that it was difficult to make them eat this meal. The reasoning of many of these subjects was: "Since I have eaten essentially nothing at two-thirds of the meal times, there does not need to be much restriction during the other times."

When 96 patients were questioned concerning the three articles of diet which did most to cause their obesity, sweets, bread, and potatoes were listed far more frequently than were any of the others. However, there were distinct individual variations. Whereas some subjects stated that they had a very strong desire to eat a pound of candy at once, others stated that they had absolutely no desire for candy and had eaten none for many months. Certain patients ate large quantities of butter, mayonnaise, gravy, etc., while others had very little desire for them. Many subjects were of the impression that the excessive ingestion of water played a significant part in the development of their obesity. Thirty-five patients believed that they drank distinctly more water than did normal individuals. This characteristic was probably the main factor accounting for the nocturia which 63 per cent of them experienced.

Many patients stated that they did not eat very much food, but calculation of the caloric intake showed that they were consuming much larger quantities than they had realized. Not infrequently there was a marked misconception of the relative caloric value of foods. In some instances the volume of food was relatively small, but it was rich in calories. Moreover, the amount that they were eating between meals was often much greater than they appreciated. Overeating was spasmodic in some patients. They restricted their

eating for several days and then went on an "eating splurge" for one or two days.

4. *Metabolic Rate.* The law of conservation of energy must be respected in correlating the number of calories ingested with the deposition of adipose tissue. The body metabolizes enough food to supply the amount of energy required. When an excess of this energy source is ingested it is stored as carbohydrate, protein and, especially, as fat. Markedly obese subjects generally metabolize more food when in a basal state than do normal individuals, but when the oxygen consumption is expressed in terms of the surface area of the body, there is no significant difference in the two groups. Thus, the basal metabolic rate of obese patients tends to be normal. However, the rate of metabolism fluctuates markedly throughout the 24 hours of the day in accordance with various activities, especially the amount of physical exertion and the emotional reactions.\* In a number of our subjects who became obese the daily activities were generally less than normal, although they did not eat any more food than did normal individuals. Earlier needs for a large intake of calories, as for example in athletes, were often not followed by a reduction in food when a sedentary existence was assumed, the individual having continued to eat until the previous sensations of fullness and satiety were obtained.

5. *Question of Dysfunction in the Assimilation and Metabolism of Food.* A question that still arises in the minds of many patients and some physicians is whether obesity results from a qualitative alteration in the manner of handling food in the body. Much evidence has been accumulated<sup>2,3</sup> to indicate that obese individuals (a) do not have greater efficiency in digestion, (b) do not absorb a greater proportion of ingested food than do normal subjects, and (c) do not have a qualitative defect in the storage and utilization of fat, nor in the conversion of carbohydrate to fat.

6. *Injury to Hypothalamus.* Ranson and associates<sup>6</sup> showed that injury to a specific portion of the hypothalamus in rats led to the production of marked obesity. Brobeck and colleagues<sup>7</sup> demonstrated that in animals so treated the weight gain depended entirely upon the increase in food consumption; these rats used fats normally when fasting. Moreover, the oxygen consumption was the same as in normal animals of the same weight.

Eleven per cent of our obese subjects had had severe injuries to the head, as compared to two in the control group. One patient, aged 20, stated that she was slightly underweight until the age of 10, when she was hit by an automobile and received a fracture of the skull. On the day of injury she developed an insatiable desire for food and rapidly gained weight until she weighed 313 pounds. Another patient, aged 42, was underweight and of short stature until the age of 10, when she fell off of a ladder, landing on her feet. The following day she developed a pronounced hunger which persisted. Her weight increased to 270 pounds.

\* Mentation is generally stated not to cause much oxygen consumption. However, when the nature of mentation is such as to provoke pronounced emotional reactions, the oxygen consumption may be increased enormously.

In the other patients receiving injuries there was not a definite association of hyperphagia with the injury.

7. *Endocrinopathies.* Endocrine abnormalities are often said to be the basis of obesity. However, the evidence indicates that endocrinopathies are rarely the cause of more than mild obesity. When obesity does occur in such cases it results chiefly from the imbalance of energy output and intake.

### A. Clinical Studies

a. *Pituitary.* Individuals with hypopituitarism, unassociated with hypothalamic injury, usually are of normal or subnormal weight. Individuals with Froehlich's disease may be quite obese, but the primary injury in this entity is not in the pituitary gland. With hyperpituitarism, as with acromegaly or Cushing's disease, the subject rarely becomes more than slightly obese. Moreover, most obese subjects do not have the clinical picture of these endocrine diseases.

b. *Thyroid.* Hypofunction of the thyroid gland has often been designated as the cause of obesity, but much evidence has been produced to refute this view.<sup>2</sup> Estimation of the basal metabolic rate was made in 69 of our patients; in 61 the rate was found to be between  $-10$  and  $+10$  per cent. The values obtained in the other patients were  $-13$ ,  $-15$ ,  $-16$ ,  $-17$ ,  $-22$ ,  $+11$ ,  $+15$ , and  $+22$  per cent. Eleven of 24 obese patients, unselected, were found to have less than  $4 \gamma$  of protein-bound iodine per 100 c.c. of plasma,<sup>8</sup> but in view of the clinical picture, the essentially normal basal metabolic rates, the insignificant response to treatment with from 1 to 2 grains (U.S.P.) of desiccated thyroid daily, and the infrequency of significant obesity in myxedematous patients, thyroid deficiency does not seem to be a very significant cause of obesity.

A few patients with thyrotoxicosis and some obese subjects treated with desiccated thyroid gain weight, presumably as a result of the increased appetite.

c. *Adrenals.* Recent observations<sup>9, 10</sup> have indicated that certain of the adrenal steroids promote the accumulation of fat in the body. These studies are quite interesting, but more information is needed to ascertain whether these steroids are of significance in the etiology of the usual type of obesity.

Most patients with Cushing's disease are obese, but rarely is the obesity marked. The obesity in this disease is probably related partially to the excess amount of glucose available with supposedly an adequately supply of insulin. The peculiar configuration of the body is due partially to the loss of protein structure along with fat deposition and to postural changes. Moreover, the adiposity has a characteristic distribution in the body. Not many of the classical manifestations of Cushing's disease are present in the average patient with obesity.

Estimation of the 17-ketosteroid excretion in 18 markedly obese adult female patients, below the age of 55, showed a decreased excretion in 9

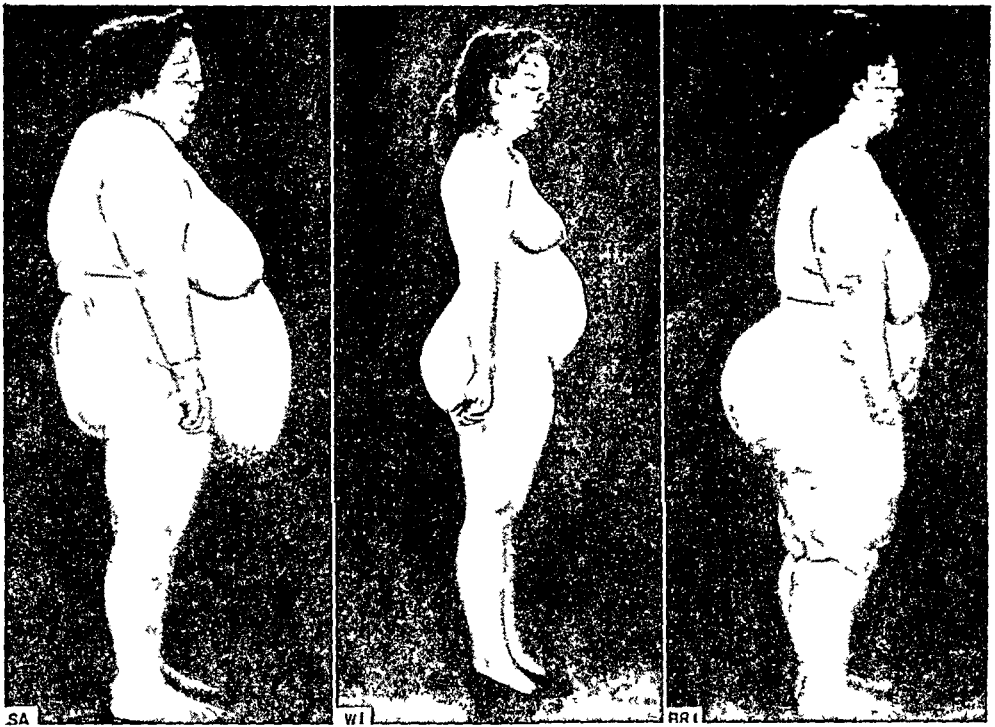


FIG. 2 Note the variation in distribution of fat.

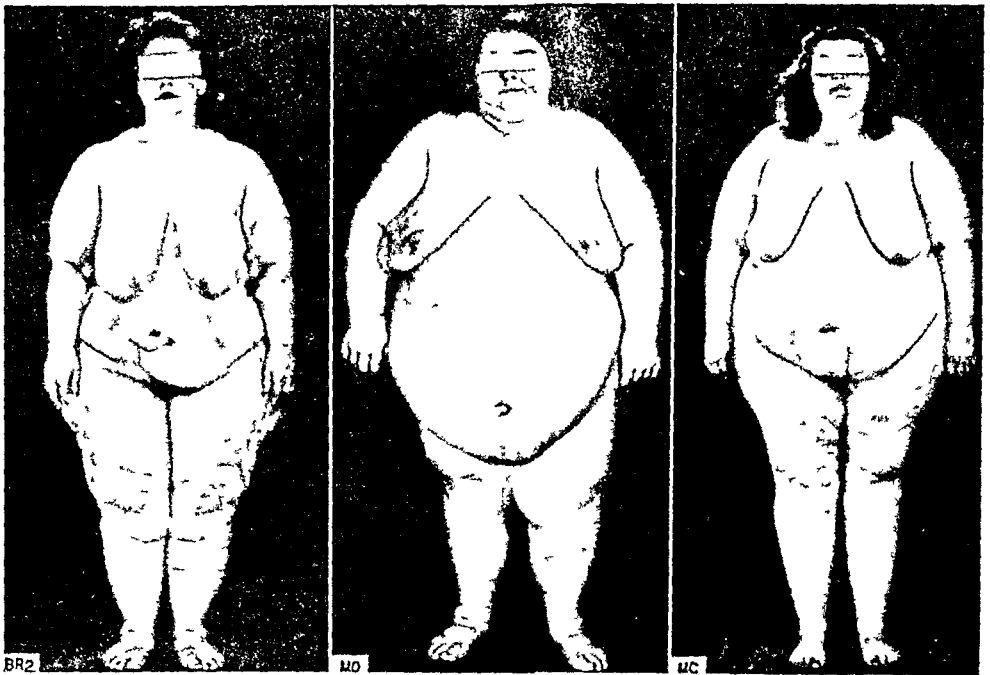


FIG. 3. Note distribution of fat. Patients BR and MC specifically related the onset of hyperorexia to cranial injury. Patient MO had become bed-ridden from her obesity.

(below 5 mg. per 24 hours) and an increased excretion in 1 (17 mg.). The "cortin" excretion was normal in each of 11 patients.

d. Gonads. Many hypogonadal individuals, male and female, are somewhat obese, but there are many others who have very little or no obesity. Although there is a tendency for obese patients to have secondarily decreased gonadal function, in most of the cases this is slight. Of the 34 married obese women whom we studied there was an average of three pregnancies.

e. Pancreas. Hyperinsulinism may produce hyperphagia and thus obesity, but this entity is rare.

## B. Animal Studies

In a separate study<sup>8</sup> the amount of fat in the entire body of rats was estimated at intervals of from three to eight weeks after removal of the pituitary, thyroid, pancreas, adrenals, testes or ovaries, but the fat was found to be increased either very slightly or not at all. Moreover, the administration to normal rats, for intervals of more than three weeks, of thyrotropin, adrenotropin, pitressin, desiccated thyroid, cortin, adrenalin, lipocaic, insulin, progesterone, estradiol, diethylstilbestrol or testosterone did not cause significant increase in fat.

## FAT DISTRIBUTION IN PATIENTS

The distribution of fat varied a great deal, as indicated by figures 2 and 3 and table 2. It was amazing to observe how enormous accumulations of fat occurred in some regions, without there being much increase in other areas. In other patients, the relative quantities of fat in these sites were found to be reversed. In the markedly obese males most of the excess fat was in the abdomen and, to a lesser extent, on the chest. In addition to having a great deal of fat in these areas, the female patients often had marked accumulations in the gluteal region, hips, thighs and breasts.

The heights of the patients were of about normal average.

The blood pressure was more than 140 systolic and 90 diastolic in 20 of 130 patients. (Thirty-nine per cent of the obese subjects, compared with 4 per cent of the controls, stated that at least one of their parents or siblings had hypertension.)

## TREATMENT

The preceding data have been presented in order to serve as a basis for rational therapy in obesity. Until shown contrariwise, it seems feasible to assume that ordinary obese subjects assimilate and metabolize their food in the same manner, qualitatively, as do normal individuals. It is clear that obesity develops because the fat and fat-precursors are ingested more rapidly than the fat is metabolized. There is a positive calorie balance involving fat, and to some extent, carbohydrates and proteins, since they contribute to the accumulation of fat. When the daily ingestion of calories is below the

TABLE II  
Relative Increase in Amount of Fat in Certain Areas of the Body

[illegible]

\* Males.

++ = slight excess; +++ = massive amount of fat.

demands of the body for energy, the stores of carbohydrates, fats and proteins are, in order, preferentially metabolized. Therefore, in the treatment of obesity it is clear that a negative calorie balance must be produced and this can be accomplished only by reducing the energy intake (food) or by increasing the energy output.

A. *Therapy Causing Increased Expenditure of Energy.* The chief methods that have been proposed for increasing the energy output are the administration of (a) desiccated thyroid, (b) dinitrophenol, (c) stimulation of the central nervous system (atropine, caffeine, 2-aminopropanes, etc.), and (d) increased exercise. When effective in reducing weight, each of these methods usually produces hypermetabolism. Since many obese subjects are less energetic than the average non-obese individual, increased mental and physical activity are probably desirable in many patients. However, such is not desired in some individuals with cardiovascular disease and certain other complications. Much more exercise is needed to produce weight reduction than is often realized. Some of Newburgh's illustrations<sup>2</sup> make this very emphatic. For example, it is estimated that a patient weighing 250 pounds will have to climb 20 flights of stairs to expend the energy contained in one slice of bread and he must walk 26 miles to rid himself of 1 pound of adipose tissue!

When the good and bad effects are evaluated, these therapies are not generally very satisfactory, with the exception of certain aminopropane derivatives discussed later. Some patients lose a great deal of weight with desiccated thyroid therapy, when given in doses of approximately 3 grains daily. However, others may be bothered with headache, nervousness, dizziness and palpitation and may not lose much weight. We have seen several individuals who had taken desiccated thyroid with subminimal dietary requirements who developed Graves' disease and we consider that there is possibly a causal effect in these cases. Contrary to Evans' viewpoint,<sup>3</sup> we believe that desiccated thyroid offers more promise when given to children who are obese and have delayed puberty, even though they may have a normal basal metabolic rate. It is even more desirable if such adolescents are also of short stature. The beneficial effects of thyroid in this situation seem, however, to be due more to its augmentation of growth and maturation than directly to a hypermetabolic effect.

B. *Therapy Causing Decreased Intake of Calories.* Measures directed toward decreasing the caloric intake are more effective in treating obesity than are ones producing hypermetabolism. They have consisted of (a) the use of cathartics (decreasing the absorption of food), and (b) decreasing the ingestion of calories. The first of these measures is quite unsatisfactory. The latter is the most effective form of therapy, but usually necessitates far more than to tell the patient to "cut down on your sweets, potatoes, pastries, and butter," and necessitates more than to hand him a diet sheet with didactic instructions. The factors which contributed to the patient's obesity must be ascertained, explained to him and corrected. However, the patient may

not appreciate this aid until he has become convinced of the ill effects of marked obesity. He must know that this condition may interfere markedly with his social and economic attainments, his health, his life expectancy and his general happiness. Thus he must learn "the price of obesity." Moreover, he should become determined not only to lose the extra weight, but to prevent its recurrence. He should know that it will probably be necessary to observe certain precautions in eating for the rest of his life. Such convictions are necessary regardless of the type of therapy employed.

He should also be convinced early in the course of therapy that no matter how little he has been eating, or whatever contributory factors may have existed, his consumption of calories, in excess of his energy output, should be eliminated. Some of the facts that should be clarified in the patient's mind may be summarized as follows: (a) Overindulgence in food "just to be sociable" may ultimately defeat its own purpose, leading to a somewhat asocial state. (b) When obese subjects eat more food than they want and need, "just to clean the plate," they should visualize themselves as a greasy garbage can—the repulsive effect is desired. (c) Sensual pleasures leading to obesity should be replaced by habits less costly to health. (d) Excess eating as a mechanism of compensation for unhappiness should be corrected, if possible, by helping the patient to make satisfactory adjustments to his emotional distress. (e) The body requirements for energy vary greatly in different individuals and even in the same individual under varying circumstances, and the amount of food ingested must be adjusted accordingly. (f) Desire for non-fattening foods can be created. (g) The patient should become familiar with caloric content of food and should adhere to the regimen of eating, exercise, etc. prescribed. (h) *There are no magic drugs that can satisfactorily bring about weight loss in the face of continued ingestion of excessive food.*

### 1. *Instructions Concerning Diet.*

The caloric value of the diet of choice varies a great deal in different patients. Some patients follow a diet which is of very low caloric content better than one of moderate amount, because the greater weight loss associated with it makes it more "worth the effort." Strong and associates<sup>11</sup> found that diets of only about 400 calories daily could be given for several weeks, provided that one gram of protein per kilogram of ideal body weight and about 75 per cent of this amount of carbohydrate is given daily. All of the essential amino acids must be given. A diet of only moderate bulk is desired. It is wise that the patient learn the relative caloric value of foods and that he be permitted to have a wide field of selection, especially if he eats with many other people who do not restrict their calories. However, patients who are not very intelligent or who do not exercise their willpower very much are usually given less latitude in choosing the articles of diet. The patient should eat three meals a day, eating lean meat or fish, egg, milk,



fresh fruit and two vegetables daily. The vegetables should be chiefly in the "5 per cent" class. The patients with marked obesity should avoid sugar, potatoes, candy, pastries, fatty foods. Mineral oil may be used for frying. When diets of from 400 to 600 calories are used for several weeks we supplement them with vitamins A and D and the B-complex. For diet lists and detailed instructions the reader is referred elsewhere.<sup>2,3</sup> A loss of from one to two pounds per week is perfectly satisfactory for most of the patients. In some of the tremendously obese subjects it is best to hospitalize them and then a reduction in weight of from three to five pounds per week can be produced.

## 2. Anorexigenic Drug Treatment.

In spite of spending a great deal of time in following the principles which we have presented thus far, we found that there was an appreciable number of obese patients who remained obese during intervals of several years. Of course, they had not completely followed the regimen prescribed. They failed to lose a significant amount of weight or to maintain weight loss in spite of ardent persuasion. Therefore, it was evident that some other type of therapy was necessary. We had used "Benzedrine" in several hundred patients during the previous eight years and had found it to be quite effective

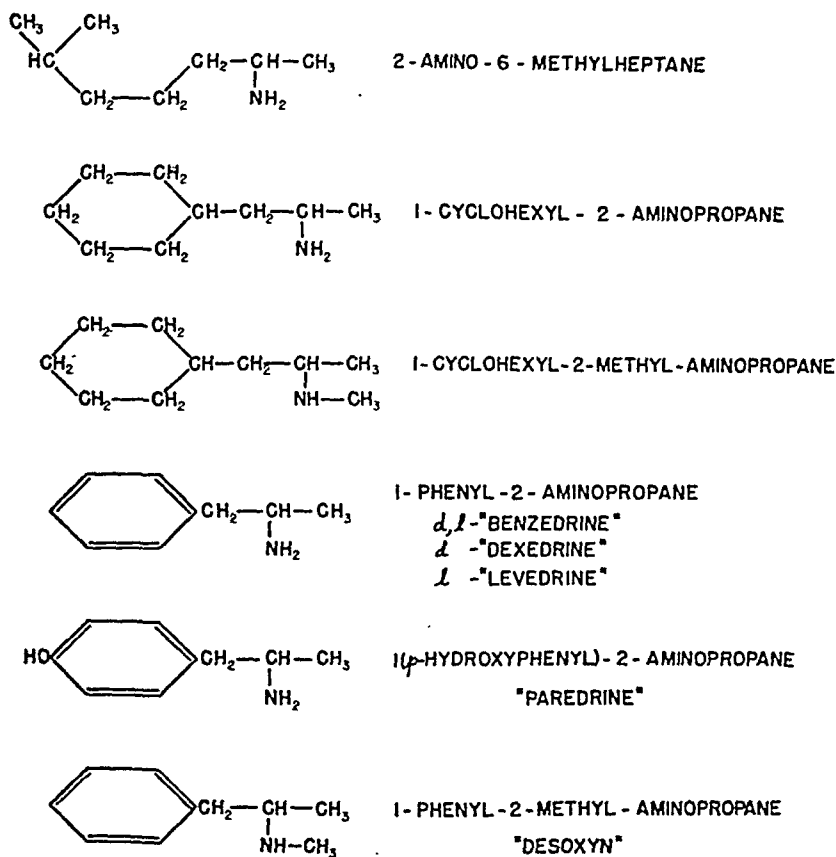


FIG. 4. Note that all of the compounds can be considered as having an aminopropane radical. Slight variations in structure greatly altered the effect of the compounds.

in promoting weight loss. However, it could not be used satisfactorily in some patients because of its side-effects. Moreover, certain others who took it very enthusiastically at first did not desire to take any more after an interval of several weeks, complaining of such symptoms as nervousness, "crankiness," dizziness, insomnia, depression, and prostration. Consequently, we began investigating other 2-aminopropanes with the hope of discovering ones with the good effects of "Benzedrine" and fewer undesirable reactions.

*Compounds Studied and Patients Treated.* The compounds used in this study are enumerated in figure 4,\* along with the structural formula of each. The structure is basically very similar, the 2-aminopropane radical presumably being an essential portion of the molecule.

A total of 132 patients, of whom 117 were females, was treated. The ages ranged from 13 to 63. Essentially all of the patients were from 50 to 200 pounds overweight. None of them had frank glandular disease, other than diabetes mellitus. Hypertension, heart failure, cerebrovascular accidents, diabetes mellitus, nephritis, epilepsy, and peptic ulcer were complications that existed. Only 18 per cent had not had some form of anti-obesity therapy previously. The other 82 per cent had been treated periodically for several years with diet, thyroid and "Benzedrine." Thirty-five per cent had been treated with "Benzedrine" and 31 per cent with desiccated thyroid. Most of these patients had concluded that they would always remain obese. A good many subjects had become so incapacitated that they had stopped working.

TABLE III  
Courses of Therapy with Each Compound

Compound	No. of Courses
1-cyclohexyl-2-aminopropane	96
d, 1-phenyl-2-aminopropane	73
l, 1-phenyl-2-aminopropane	10
d, l, 1-phenyl-2-aminopropane	10
2-amino-6-methylheptane	25
1-cyclohexyl-2-methyl-aminopropane	32
1-phenyl-2-methyl-aminopropane	36
1(p-hydroxyphenyl)-2-aminopropane	25
Total	307

*Plan of Therapy.* A total of 307 courses of therapy was given with the 2-aminopropanes described below, each course varying from two weeks to one year. Fifteen patients were given from six to ten courses with from four to seven compounds. 1-Cyclohexyl-2-aminopropane and d, 1-phenyl-2-aminopropane ("Dexedrine") were used more than were the others (table 3). All therapy was given by mouth in the form of tablets or capsules in the

\* We are grateful to the Abbott Laboratories, North Chicago, Illinois for supplying us with "Desoxyn" and to the Smith, Kline and French Laboratories, Philadelphia, Pennsylvania for the other compounds studied.

dosage ranges shown in table 4. Usually two doses per day were prescribed. One dose was given at 10 or 11 a.m. and one at 3 or 4 p.m. The morning dose tended to be larger than the afternoon one. Since most of the patients ate very little breakfast, it did not seem worthwhile to give treatment before this meal. Moreover, with the above dosage schedule an anorexigenic effect was present throughout the 24 hours. In a few individuals it was difficult to inhibit bed-time eating without producing insomnia. Although the greatest weight reduction can be obtained by prescribing a low calorie diet as well as anorexigenic compounds, in this study such a diet was prescribed for only a few patients, since we were interested chiefly in comparing the anorexigenic effect of the several compounds. Therefore, the amount of weight lost, together with the patient's statements of the subjective reactions, served to indicate the relative effects of the compounds. None of the subjects was told what medicine he was receiving. It was possible to evaluate the relative value of the compounds fairly well since several of the compounds appeared identical, some were changed alternately from capsule to tablet form without the patient's knowledge of their identity, the compounds varied in potency, the responses were somewhat proportional to the dosage, and since there was a good deal of rotation in the drugs given to individual patients.

TABLE IV  
Dosages of Compounds

Compound	Total Daily Doses (mg.)				Order of Choice
	Range Tested	Large Doses		Optimal Maximal Dose	
		Range	No. of Patients		
<i>d</i> , 1-phenyl-2-aminopropane	5-50	30-50	19	20	1
1-cyclohexyl-2-aminopropane	50-250	200-250	24	150	2
1-cyclohexyl-2-methyl-aminopropane	50-250	200-250	30	200	3
1-phenyl-2-methyl-aminopropane	5-50	20-30	8	15	4
2-amino-6-methylheptane	50-200	200	5	150	5
<i>d</i> , <i>l</i> , 1-phenyl-2-aminopropane	10-30	20-30	5	20	6
1( <i>p</i> -hydroxyphenyl)-2-aminopropane	20-100	60-100	13	60	7
<i>l</i> , 1-phenyl-2-aminopropane	10-60	50-80	2	60	8

*Effects of Treatment.* All of the compounds used had good or bad effects or both in most of the individuals. These varied markedly with different drugs, with the same drug given to different individuals and sometimes with the same drug given in the same dosage to the same individual. Only slight changes in the structure of the compounds caused marked change in the biological effects. The desirable effects consisted of anorexia, increased mental and physical activity, a sense of well-being, more ambition and determination and less fatigue. Undesirable reactions observed were nervousness, apprehension, depression, insomnia, exhaustion, headache,

dizziness ("light-headedness"), unpleasant taste, halitosis, burning in throat, heart-burn, dryness of mouth, nausea, vomiting and increased frequency of bowel movements. Other symptoms noted were increased or decreased sweating, increased or decreased thirst, diuresis, general numbness, cold feeling, crawling sensation, rash and tachycardia. A statistical analysis of the frequency of individual symptoms produced by the compounds was unsatisfactory because of variations in dosage and of vagueness in their manifestations. Frequent determinations of the blood pressure were made. In a few cases slight and transient increase in the pressure resulted.

All compounds produced similar manifestations, but the relative intensity of the symptoms varied considerably. Each compound produced in certain patients a pronounced anorexia, weight loss, feeling of well-being, more energy, less fatigue and insomnia. However, in the case of 1(p-hydroxyphenyl)-2-aminopropane ("Paredrine") and of 1, 1-phenyl-2-aminopropane ("Levedrine") the effect was exerted in only a small proportion of the patients treated and was of short duration. Some of the patients observed that the latter compound produced a very "pleasant effect" even when no weight loss was produced. The "pleasant effect" did not seem to be associated with as much of the irritating, depressing, and apprehensive action as was possessed by some of the other compounds, especially 1-phenyl-2-methyl-aminopropane ("Desoxyn") and d, 1, 1-phenyl-2-aminopropane ("Benzedrine"). d, 1-phenyl-2-aminopropane ("Dexedrine") differed from these latter two compounds in its effects upon the central nervous system. It gave the individuals a great deal of pep, ambition, feeling of well-being, and at the same time it caused a marked inhibition of the appetite. The other two compounds, in addition to having these effects, produced apprehension, irritability and lightheadedness which caused the patients to dislike them more. This dislike interfered with the administration of doses large enough to cause marked and continued inhibition of appetite. 1-Cyclohexyl-2-aminopropane exerted cerebral effects somewhat similar to those of the aforementioned two compounds, but it was better tolerated. 1-Cyclohexyl-2-methyl-aminopropane had less of the undesirable cerebral effects than 1-cyclohexyl-2-aminopropane, but, on the average, its anorexigenic effect was not as potent. 2-Amino-6-methylheptane did not cause as many cerebral ill-effects as did "Benzedrine" or "Desoxyn" but its anorexigenic effect was less.

The "unpleasant taste" consisted of a "metallic" or "brassy" quality. Several patients believed that their "breath was bad," and some were so informed by their friends. It was more marked during the interval preceding meals. The alterations in sweating, water intake and output, numbness, cold sensation, dryness of mouth, burning in the throat, and increased bowel movements were all insignificant. Nausea was rare but did occur with each of the compounds except "Levedrine." In a few instances vomiting occurred and necessitated temporary cessation of the drug. When large doses of any of the compounds were given continuously for several months,

certain patients became nervous and exhausted and discontinued the treatment. Then they tended to sleep heavily for several days, at the end of which time they felt in good condition. It was remarkable how much difference in tolerance to the drugs existed. For example, a few patients took 50 mg. of d, l-phenyl-2-aminopropane ("Dexedrine") daily for several weeks with "no ill-effects." One patient took 50 mg. daily of 1-phenyl-2-methylaminopropane ("Desoxyn") for two weeks with no unpleasant reactions. Similar experiences were obtained with the other compounds. However, most of the patients who received doses equal to the upper range, indicated in table 4, or slightly greater, were bothered by such symptoms as restlessness, anxiety, fullness in the head, headache, dizziness, insomnia, depression and nausea.

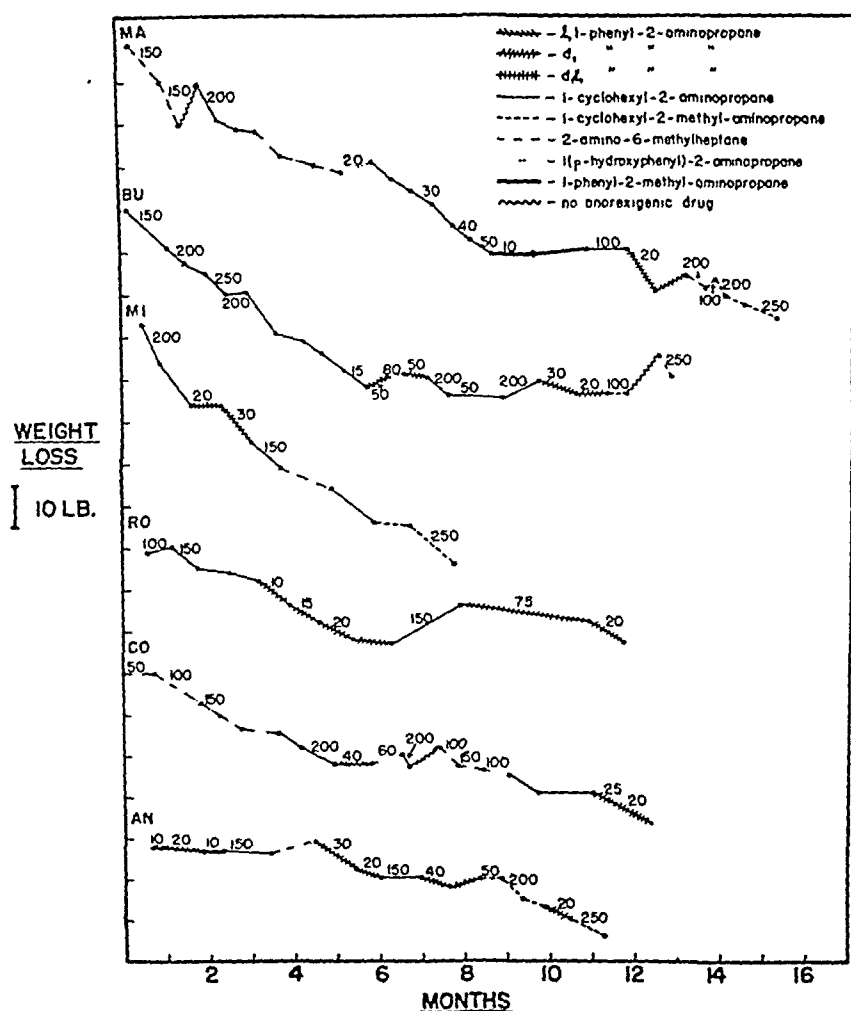


FIG. 5. The size of the doses is indicated in mg. by the numerals and was unchanged until the succeeding segment bearing a numeral. Note the variability in response of individuals to different drugs and even in the same subject at different times. A state of refractoriness sometimes developed after several weeks, but after stopping treatment for a few weeks or changing to another compound much of the effectiveness was restored. Most of the patients were not prescribed an anti-obesity diet. Patient AN had more refractoriness in her response than any of the others.

*Late Effects.* After taking any of the compounds for several weeks, it was observed that the effects were sometimes much less (figures 5 and 6). By increasing the dosage there was an augmentation of its action, but sometimes a stage was reached when even large doses were without significant effect and if continued they tended to make the patient exhausted. The larger was the initial dose, the sooner did this state of refractoriness develop. Then upon changing therapy to another compound a striking effect was often produced, but after several months a state of refractoriness to the second drug was developed. If therapy with the first drug was resumed, there usually was a much greater effect than at the time of its discontinuance, but not as great as at the time that it was first administered. Sometimes a state of refractoriness to all of the compounds listed in figure 4 developed. After an interval of from 3 to 15 weeks, the initial sensitivity to the compounds was largely regained. No difficulty was encountered in getting the patients to take periods of rest from therapy. Some of their dislike for being without the anorexigenic and stimulating effects of the compounds during these rest periods was relieved by their knowledge that the effects would be increased with the resumption of therapy. No instance of definite habit formation for the drugs was observed. All of the ill-effects of the compounds disappeared within a few days after stopping therapy. There was a distinct variation in the amount of refractoriness developed in different patients. Some patients continued to get the same good effects from the same drug for more than six months. It is desirable to stop therapy with the anorexigenic compounds as soon as the patients lose weight adequately without them; this interval varies from a few weeks to many months.

*Selection of Most Effective Anorexigenic Compound.* The selection of the best of the aforementioned compounds for the treatment of obesity seems to depend chiefly upon the amount of loss of weight which it produces considered in conjunction with the ill-effects which it provokes. In this situation it does not make much difference about the relative size of the dosage. For example, even though drug "A" may have to be used in quantities 10 times greater than drug "B" to produce the same amount of weight loss, if drug "A" caused fewer ill-effects at the stated dosage it would be preferable, at least pharmacologically.

The patient's conclusion on the subject is highly important, but it must be considered in conjunction with an analysis of its individual effects. A compound which produced only a moderate loss in weight, but permits the patient to be energetic, happy and rested is much better than one which promotes marked weight loss, but also causes restlessness, irritability and insomnia. The patient may take the latter type of compound for several weeks, but at the end of this interval he feels exhausted and somewhat frustrated, so he will decide not to take any more of this type of therapy. On the other hand, although a patient takes a compound which produces certain pleasant sensations and no significant unpleasant ones, if not much weight is lost, he, as well as the physician, will become very much dissatis-

fied with this type of treatment. Moreover, it must be borne in mind that there is a distinct variation in the effectiveness of the compounds in different individuals. For example, a compound which has many good effects and few bad manifestations in one individual may in another individual have few good effects and many bad ones, while in a third subject not much of either effect is obtained. However, considering all of these features, we have indicated in table 4 our order of preference of the compounds. The last two chemicals listed are much less effective than the others, although there is a similarity in structures. d, 1-Phenyl-2-aminopropane ("Dexedrine") is the drug of choice because in most of the patients it produces a moderate anorexigenic effect, yet the unpleasant effects are mild or absent. As far as the others are concerned, it must be remembered that one cannot predict with accuracy in a given patient which one will be most effective and, moreover, it is often wise to shift to other compounds when a state of refractoriness develops. Certain patients became refractory to daily doses as great as 50 mg. of d, 1-phenyl-2-aminopropane ("Dexedrine"), 200 mg. of 1-cyclohexyl-2-aminopropane, 250 mg. of 1-cyclohexyl-2-methyl-aminopropane, 200 mg. of 2-amino-6-methylheptane, 100 mg. of 1(p-hydroxyphenyl)-2-aminopropane ("Paredrine") and 50 mg. of 1, 1-phenyl-2-aminopropane ("Levedrine").

*Selection of Dosage.* The appropriate dosage of the drugs is one which will bring about a loss of about 1 pound or more per week and yet will not produce enough unpleasantness to interfere with prolonged usage. Only the minimal amount of the compound which is necessary to produce the desired amount of weight loss should be used, since the large doses tend to produce a state of refractoriness sooner than do the small doses and involve an unnecessary expense. In table 4 we have recorded what we consider to be an optimal maximal daily dose of each compound tested. Some individuals took larger doses satisfactorily, while others could not take doses of the size listed. Most of the patients tolerated these doses well for several weeks and experienced a distinct anorexigenic effect. In many instances doses which were only from 50 to 75 per cent of these were satisfactory. The specific dosage had to be regulated in each patient.

*Mechanism of Action.* The chief mechanism by which the 2-aminopropanes produce a loss of weight is by decreasing the hunger and appetite<sup>12</sup>—an anorexigenic effect. Essentially all of the patients had a decrease in their desire for food throughout the entire day. In this connection it was observed that four patients who were kept in the hospital on a low calorie diet, maintained meticulously constant, lost weight just as rapidly when they were not taking any anorexigenic compound as when taking large doses of them (figure 6 and 7). We found that none of these compounds increased the basal metabolic rate. However, they must increase the total daily consumption of calories as evidenced by the increase in mental and physical activities that are produced. The increase in ambition, determination and feeling of well-being may help the patient to make adjustments in his habit of over-

eating and correct some of the factors which contributed to this habit. In most of the patients, with the usual dosage employed, the decrease in appetite is best not thought of as a toxic effect, since the patient tended to feel better than usual and the ill-effects were generally mild and reversible.

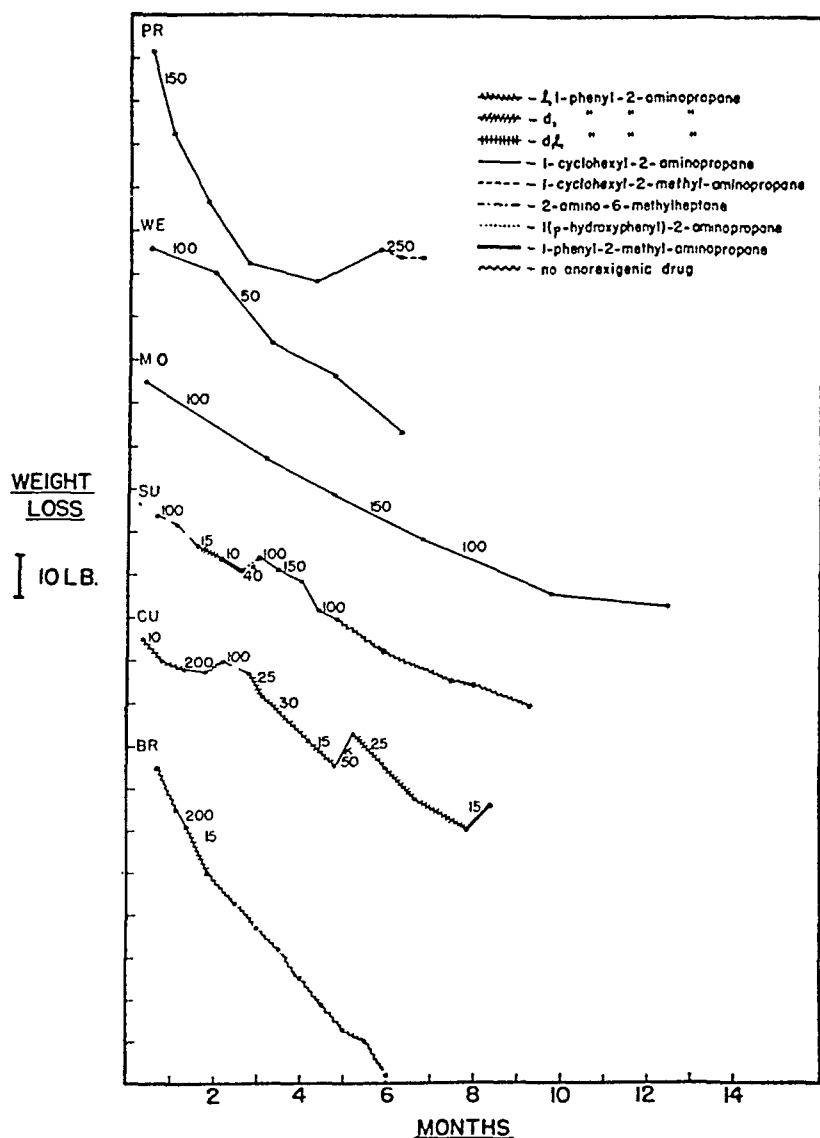


FIG. 6. Note that patients SU and BR lost weight just as rapidly without the anorexigenic compounds as with them. These patients, however, were maintained on low calorie diets. Patient MO took the same compound for a year with equal effectiveness throughout the interval.

There may have been a slight effect on the gastrointestinal tract since some of the patients had an increase in the number of bowel movements, a few experienced nausea and a very few complained of abdominal pain. A few individuals stated that they "went to the table about as hungry as usual.



but found that it took less food to produce a full feeling." There was no significant change in the volume of the stools.

Effects of the compounds upon the volume of urine were inconsistent. During the first few days there tended to be a slight diuresis.

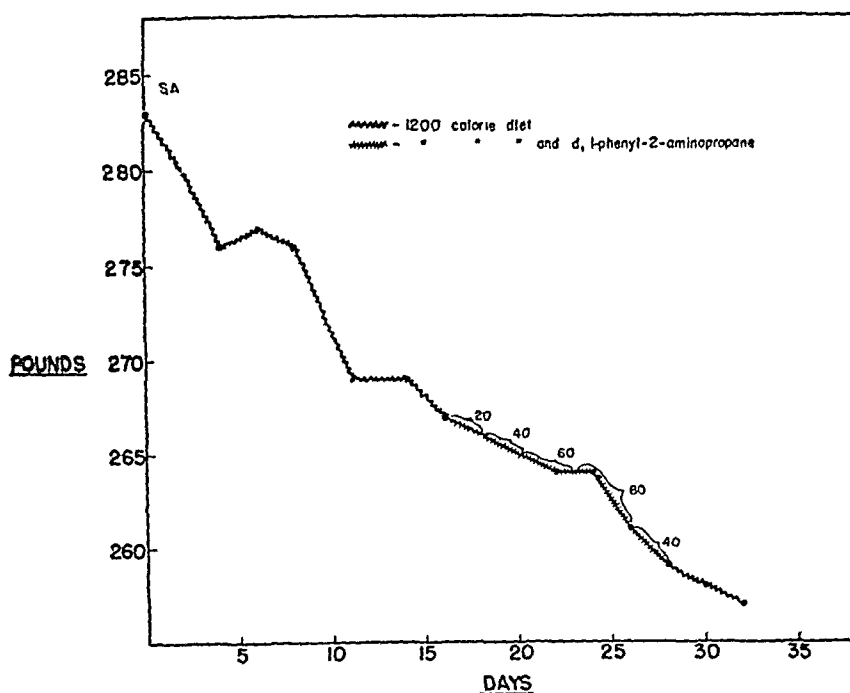


FIG. 7. Note that patient SA lost weight just as rapidly on a carefully controlled 1200 calorie diet as she did with d, l-phenyl-2-aminopropane given in large doses in conjunction with the same diet.

Several patients volunteered the comment that most of the weight lost while taking the drugs was from their waist and that the amount of reduction of the circumference of their waist was greater than the amount of weight lost would indicate. For example, one subject had a decrease in waist circumference of 6 inches with a loss in weight of only 24 pounds.

### SUMMARY AND CONCLUSIONS

Marked obesity interferes seriously with the health and happiness of a vast number of individuals. This fact should be clarified in the minds of obese subjects and their desire to take adequate therapy should be stimulated. Although obesity should be conceived of as a condition of positive energy balance, the factors which contribute to this imbalance, whether emotional, environmental, etc., should be sought and corrected as far as is possible. The patient should learn about relative caloric values of many articles of diet and should have his daily ingestion of food restricted sufficiently to lose the desired amount of weight.

If these objectives are not obtained after the physician has made an ardent effort to pursue the principles just outlined, it is often of advantage

to use compounds of the aminopropane type as adjunctive therapy. These compounds are of aid chiefly through their anorexigenic effect. Consequently, it is quite important that a diet of low caloric value is prescribed and that the patient follow the other features of regimens outlined for obese subjects not receiving drug treatment. The use of the anorexigenic compounds alone does not cause sufficient loss of weight in most subjects.

In this clinic we have used 8 aminopropane compounds in the treatment of 132 markedly obese patients. A total of 307 courses of therapy, from 2 to 52 weeks, was administered. A few patients received as many as 10 courses with 7 different compounds. For this study most of the patients were not placed on a special diet, since it was desired to observe the effects on weight reduction of the drug alone.

Individuals were found to vary a great deal in their response to the different compounds and even the same compound; moreover, a variable degree of refractoriness was found to develop. All of the compounds used had good effects, or bad effects, or both, in most of the patients. The good effects consisted of anorexia, increased mental and physical activity, a sense of well-being, and increased ambition. Undesirable effects were restlessness, apprehension, depression, irritability, insomnia, exhaustion, headache, dizziness, unpleasant taste, halitosis, burning in the throat, dryness of mouth, heart-burn, nausea, vomiting and increased frequency of bowel movements. By the appropriate regulation of the dosage most of the patients were made to lose a significant amount of weight without the ill-effects of the compound being very prominent. Considering all of the characteristics of the chemical used, the following three drugs, in order of preference, were chosen as the most desirable ones: d, 1-phenyl-2-aminopropane ("Dexedrine"), 1-cyclohexyl-2-aminopropane, and 1-cyclohexyl-2-methyl-aminopropane. In some patients it is not necessary to use drug therapy for more than a few weeks, because the patient will have become adjusted sufficiently well to continue the regimen without it. When it is necessary to administer the compounds for many months we suggest that after treatment for intervals of about four months there be interspersed periods of from two to four weeks with no anorexigenic drugs. When a state of moderate refractoriness has developed, another one of the compounds should be used. The first compound can later be used effectively.

The good effects of this type of treatment greatly overbalance the ill effects when it is used cautiously in selected cases.

#### BIBLIOGRAPHY

1. DUBLIN, L. I., and LOTKA, A. J.: *Length of life*, 1936, The Roland Press Co., New York.
2. NEWBURGH, L. H.: *Obesity*, *Arch. Int. Med.*, 1942, lxx, 1033-1096.
3. EVANS, F. A.: *Obesity, from Diseases of metabolism*, edited by G. G. Duncan, Ch. X, 1947, W. B. Saunders Co., Philadelphia.
4. WILDER, R. M.: *Regulation of the weight of the body*, *Internat. Clin.*, 1932, i (Series 42), 30-41.

5. DUBLIN, L. I., and MARKS, H. H.: Mortality of women according to build, *The Assoc. of Life Ins. Med. Directors of Am.*, Oct. 20, 1938.
6. RANSON, S. W., FISHER, C., and INGRAM, W. R.: Adiposity and diabetes mellitus in monkey with hypothalamic lesions, *Endocrinology*, 1938, xxiii, 175-181.  
HETHRINGTON, A. W., and RANSON, S. W.: Experimental hypothalamico-hypophyseal obesity in rat, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 465-466.
7. BROBECK, J. R., TEPPERMAN, J., and LONG, C. N. H.: Effect of experimental obesity upon carbohydrate metabolism, *Yale Jr. Biol. and Med.*, 1942-43, xv, 831-853.
8. WILLIAMS, R. H.: Unpublished data.
9. KEPLER, E. J.: Symposium on the synthesis and biological action of the adrenal hormone dehydrocorticosterone, March 11, 1946, Atlantic City, New Jersey.
10. HARTMAN, F. A., BROWNELL, K. A., and THATCHER, J. S.: A new hormone of the adrenal cortex, *Jr. Clin. Endocrinol.*, 1947, vii, 461-462.
11. STRONG, J. M., McCLUGAGE, H. B., and BROWNLEE, M. A.: The nitrogen balance during dietary correction of obesity, *Am. Jr. Med. Sci.*, 1931, clxxxi, 336-349.
12. HARRIS, S. C., IVY, A. C., and SEARLE, L. M.: Loss of weight, *Jr. Am. Med. Assoc.*, 1947, cxxxiv, 1468-1474.

# CASE REPORTS

---

## THE DISADVANTAGES OF SULFONAMIDE COMBINATIONS \*

By WILFRED CARROL, M.D., *Newark, N. J.*

RECENTLY there have appeared reports in the literature advocating the use of "sulfonamide combinations."<sup>1, 2</sup>

The purpose in giving combinations of these similarly acting drugs has been to reduce the danger of "intrarenal drug precipitation" and "concrement formation." While giving comparatively small doses of each component of a mixture of sulfonamides, the danger of intrarenal drug precipitation should be only as great as if each compound had been administered alone. Yet the sum of the components could be completely effective in eradication of a given infection. This method of sulfonamide therapy at first sight appears very desirable but a case is herewith presented that demonstrates the disadvantages of combined sulfonamide medication.

### CASE REPORT

Mr. F. L., a 58 year old building contractor, appeared in my office on February 1, 1947, complaining of burning on urination, frequency and pain at the urethral meatus. These symptoms had appeared 10 days previously and were getting progressively worse. The patient had had extramarital relations about one month before.

His past health had always been "perfect." He had had a hemorrhoidectomy in 1914. Otherwise he had never had to consult a physician.

*Physical Examination:* The patient appeared ill. He had a tachycardia, pulse 114 and temperature 100° per rectum. His blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The only pathological finding of any importance was the presence of a heavy urethral discharge. His heart was not enlarged. No murmurs were heard. No costovertebral tenderness was demonstrated. His prostate gland was normal in size.

His urine showed no albumin or sugar. Abundant pus was evident grossly and microscopically. The urethral smear showed a variety of organisms, a few gram negative intracellular diplococci and many extracellular gram negative bacilli and cocci. His blood Wassermann test was negative.

*Treatment:* The patient was given 100,000 units of penicillin G crystalline at once and this dose was repeated every three hours for three doses. To insure the eradication of his infection he was then advised to take Combisul T.D. (Sulfathiazole-Sulfadiazine Combination, Schering) 1 gram four times a day for five days.

The patient took one gram of the drug before supper and one gram on retiring. That night he also took eight ounces of citrate of magnesia of his own volition. In the morning the third dose of Combisul T.D. was taken with fruit juice. Shortly thereafter the patient began to retch and vomit. He did this continuously for two hours and he suffered a severe chill. His temperature rose to 105.2°. On examination no new physical signs were found. It was decided that the patient had had a sulfonamide fever reaction precipitated by the magnesium citrate purge and the

\* Received for publication July 31, 1947.

dehydration resultant from vomiting. Combisul was therefore stopped and the decision was made to continue treatment with penicillin. A blood count, taken at this point, revealed 31,250 white blood cells per cubic mm. with 92 per cent polymorphonuclear cells, 5 per cent lymphocytes and 3 per cent monocytes.

Penicillin 50,000 units was thereupon given intramuscularly every three hours. The urine became much clearer. The purulent discharge disappeared and the temperature went down to 99.8° within 48 hours. Penicillin orally 400,000 units daily was then substituted for the parenteral route and the drug was continued in this manner for one week. The patient meanwhile developed a new complaint. He had a great deal of pain in moving his bowels! He also continued to run a low grade fever. His temperature was 100.6° per rectum. On examination he was now found to have a large, tender, fluctuant prostate gland. A diagnosis of prostatic abscess was made and the patient was advised to have surgical drainage. Penicillin was again resumed parenterally.

On February 14, 1947, Dr. B. Rothhouse\* performed a perineal incision and drainage of the prostate. Much pus was obtained perineally and also by way of the urethra. A culture was made of this pus and a Foley retention catheter was inserted into the bladder.

Post-operatively the patient's temperature rose to 104.8° although penicillin had been continued without interruption. It was obvious that this infection was penicillin resistant. On February 16 culture of the pus from the incision and drainage revealed *Escherichiae coli* and *Enterococci faecalis*. Blood culture was negative. A test for streptomycin sensitivity was requested but unfortunately could not be done. However, the organisms in the pus were considered by the bacteriologist to be of a type that is streptomycin sensitive. Streptomycin was thus started, 0.25 gram every four hours. A favorable response was evident the first couple of days but later the temperature went up again and it stayed up between 103° and 104.6° until February 27 at which time after some 24 hours of sulfathiazole (1 gram q. i. d.) inadvertently given, the temperature dropped to 97.8°. Shortly after this the patient had a chill and his temperature rebounded to 104° with the appearance of a macular rash. This reaction was not unexpected since the patient had previously reacted to the Combisul T.D. Sulfathiazole was immediately stopped and streptomycin was now resumed in larger dosage, 0.33 gram every four hours. Later it was again increased to 0.4 gram every four hours. On these massive doses of streptomycin the patient's temperature began to come down by lysis. For the next 15 days the patient's highest temperature was only 100.6° but he had right costo-vertebral tenderness and a consistent pyuria. He also complained of being dizzy all the time (due to streptomycin toxicity). On March 17, 1947, after the patient had shown a temperature of 100° or less for four days streptomycin was stopped. The patient then promptly developed a left epididymitis and his temperature again rose to 103°. Treatment for the next week was expectant in the hope that the epididymitis and the fever would subside spontaneously. Unfortunately, however, the temperature continued to be high and on March 25 streptomycin was resumed. After 24 hours the patient still had a fever of 104°. It was then decided to try sulfadiazine alone. In view of the fact that the patient had had so much of the antibiotics and his condition was still unimproved, and since sulfadiazine had not been tried alone but only in combination with sulfathiazole to which the patient was clearly sensitive, it was considered worthwhile administering sulfadiazine cautiously with equal doses of sodium bicarbonate. The result with the sulfadiazine was remarkable. There was a critical defervescence of the fever. The epididymitis subsided, the pyuria completely cleared in 48 hours and the costo-vertebral tenderness disappeared. No signs of intolerance to sulfadiazine developed. The patient was completely cured and left the hospital on April 3, 1947. On April 22, 1947, when a follow-up examination was made, the patient showed no residual

\* Attending Urologist, Newark Beth Israel Hospital.

evidences of genito-urinary infection but he did display an unsteady gait, a diminution in hearing and he still complained of vertigo due to the streptomycin therapy. His blood Wassermann test was again found negative.

### COMMENT

The above case illustrates the disadvantages in administering a sulfonamide combination. It is reasonable to assume that while the urinary tract disturbances resulting from sulfonamides are relatively dependent upon dosage and can probably be diminished by mixtures of two or more sulfonamides with the dose of each cut in proportion, the sensitivities such as the drug rashes, the drug fevers, the hemolytic anemias and the neutropenias are not related to dosage and should be more prone to occur with such combinations. It has been demonstrated by numerous investigators that the incidence of toxic reactions in general is lower with sulfadiazine than with the other absorbable sulfonamides.<sup>3, 4, 5, 6</sup> Therefore, giving a mixture of sulfathiazole with sulfadiazine should expose the patient to a greater risk of developing a sensitization reaction than sulfadiazine administered alone.

Secondly, with sulfonamide combinations when a toxic reaction does occur, the physician is unable to determine which component drug has been at fault and he may unnecessarily abandon this very useful type of medication whereas, if he were to use the single sulfonamide, in the presence of a reaction he could always cautiously try another sulfonamide.

Since alkalinization of the urine also is very effective in reducing intrarenal sulfonamide precipitation, the necessity of using the sulfonamide combinations would appear to be limited to only such cases as could not take adequate amounts of alkali.<sup>7, 8, 9</sup>

Statistical studies of the comparative frequency of toxic reactions to sulfonamide combinations and sulfadiazine by observers in a position to treat many cases would be desirable.

### SUMMARY AND CONCLUSIONS

A case is herewith presented where a sulfonamide combination was given with a resultant severe thermal reaction. The infection was penicillin and streptomycin resistant and sulfathiazole administered alone caused a toxic reaction but sulfadiazine was completely and quickly effective in eradicating the disease. It is suggested on theoretical grounds that the administration of sulfonamide combinations will enhance the possibility of sulfonamide reactions such as drug rashes, drug fevers, hemolytic anemias and neutropenias. It would appear to be better judgment to give a single sulfonamide with adequate alkali to prevent intrarenal drug precipitation than to give sulfonamide combinations.

### BIBLIOGRAPHY

1. LEHR, D.: Inhibition of drug precipitation in the urinary tract by the use of sulfonamide mixtures. I. Sulfathiazole-sulfadiazine mixture, *Proc. Soc. Exper. Biol. and Med.*, 1945, lviii, 11.
2. FRISK, A. R., HAGENMAN, G., HELANDER, S., and SJÖGREN, B.: "Sulfa-Combination," New chemotherapeutic principle, *British Med. Jr.*, 1947, 1, 7.
3. BLANKENHORN, M. A., and VILTER, C. F.: Toxic reactions of the newer sulfonamides, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 691.

4. FINLAND, M., PETERSON, O. L., and GOODWIN, R. A., JR.: Sulfadiazine, further clinical studies of its efficacy and toxic effects, *Ann. Int. Med.*, 1942, xvii, 920.
5. DOWLING, H. F., and LEPPER, M. H.: Toxic reactions following therapy with sulfapyridine, sulfathiazole and sulfadiazine, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1190.
6. DOWLING, H. F., et al.: Relative toxicity of sulfamerazine and sulfadiazine, *Jr. Am. Med. Assoc.*, 1944, cxxv, 103.
7. SCHWARTZ, L., FLIPPIN, H. F., REINHOLD, J. G., and DOMM, A. H.: The effects of alkali on crystalluria from sulfathiazole and sulfadiazine, *Jr. Am. Med. Assoc.*, 1941, cxvii, 514.
8. GILLIGAN, D. R., GARB, S., and PLUMMER, N.: Prevention of crystalluria during sulfadiazine therapy, *Proc. Soc. Exper. Biol. and Med.*, 1943, lii, 248.
9. GILLIGAN, D. R., GARB, S., WHEELER, C., and PLUMMER, N.: Adjuvant alkali therapy in prevention of renal complications from sulfadiazine, *Jr. Am. Med. Assoc.*, 1943, cxxii, 1160.

---

## SUBARACHNOID HEMORRHAGE SECONDARY TO A TUMOR OF THE HYPOPHYSIS WITH ACROMEGALY \*

By JACK D. KIRSHBAUM, M.D., F.A.C.P., *Bakersfield, California*, and  
BERNARD M. CHAPMAN, M.D., *Chicago, Illinois*

CASES of acromegaly are infrequently encountered and when seen are looked upon as curiosities. The clinical syndrome of acromegaly was first described in 1886 by Pierre Marie, and the following year Minkowski<sup>1</sup> suggested that the disease was caused by derangement of the hypophysis cerebri. It is well known that acromegaly is associated with eosinophilic adenomas of the anterior lobe of the hypophysis. However, many cases of eosinophilic adenoma of the hypophysis do not manifest acromegalic features nor other endocrine disturbances clinically.

Although most writers<sup>2</sup> state that acromegaly occurs usually between the ages of 20 and 30 years, the author's cases have all been older, the youngest being 35 years and the oldest 74 years. The disease has not been observed to be hereditary; however, Levy<sup>3</sup> noted in a series of cases that 30 per cent showed a familial tendency. The clinical picture usually is influenced by the size of the tumor and its intimate relationship to surrounding structures.

The following case is being reported because of its unusual complication, a subarachnoid hemorrhage.

### CASE REPORT

*Clinical History.* A 35 year old white male was admitted to the University Hospital on April 6, 1938, in a state of coma.

Relatives stated that since the age of 14 the patient's hands and jaw had been large. In the past eight years there had been a marked increase in the size of the hands and jaw and his voice had become deeper. The patient had been married for 10 years and had no children. His wife stated that for the past three years his sexual power had been absent, although he had never been very aggressive sexually. The family history was negative for endocrine disturbances.

\* Received for publication November 16, 1945.

This work was done prior to entry on active duty.

He seemed perfectly well until two weeks prior to admission, at which time he began to complain of severe headaches. Heavy doses of aspirin had no effect. This was associated with a severe emotional upset caused by his mother's death. Headaches became more severe, and two days prior to entrance the patient began to have projectile vomiting. The next day relatives stated that he seemed to be sleeping most of the time, could be aroused only with difficulty, and seemed disoriented. He vomited five to six times that day. The next day he seemed worse and was brought to the hospital.

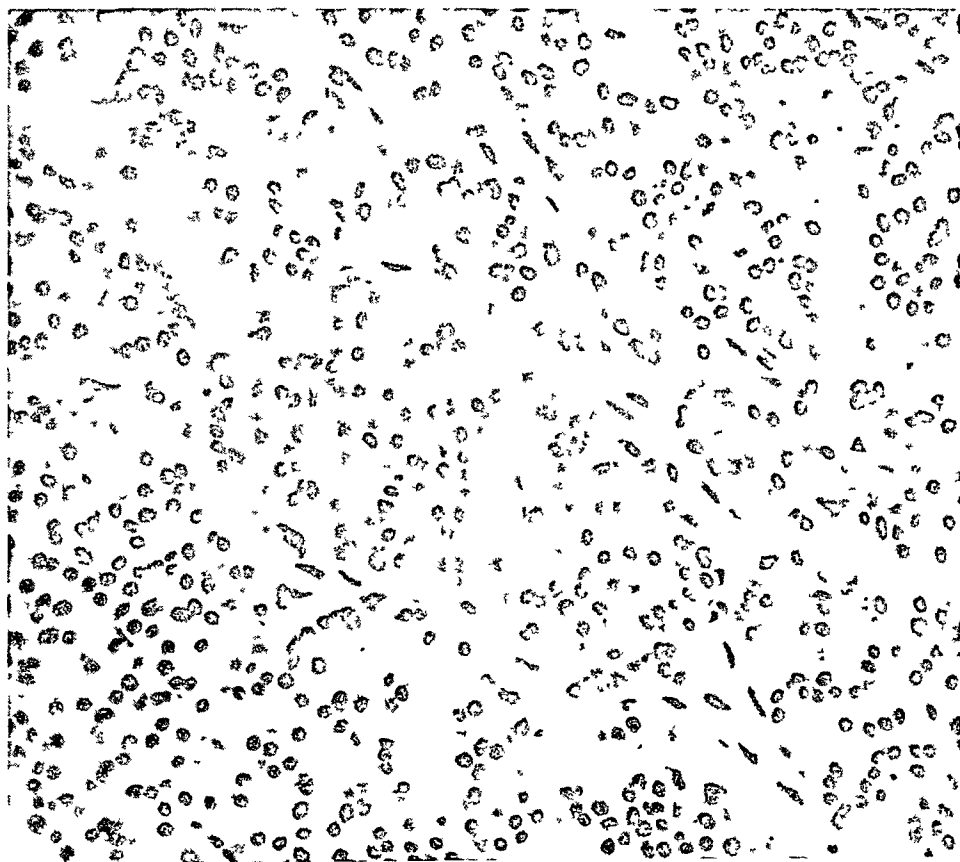


FIG 1. Section of the tumor composed of acini with fairly regular nuclei.

Physical examination revealed a well nourished, well developed white male in a semicomatose state. The facial features were typically acromegalic. The temperature was 104° F., the pulse rate was 60, and the respirations were very rapid. The head was large and the scalp was covered with hair. The nose was unusually prominent, and the pupils were equal and reacted to light. The lower jaw was large.

The neck was very rigid and the head was extended backwards. The heart tones were distant. The right lower lobe revealed bronchial breathing. The abdomen was negative. The hands and feet were very large. The fingers were sausage shaped. The back was held very rigidly. Both Kernig's and Brudzinski reflexes were strongly positive.

*Laboratory.* Urine examination was negative. The blood showed a hemoglobin of 80 per cent, red blood cells 4,170,000, and white blood cells 9,500. The Wassermann test reaction was negative. The spinal puncture revealed blood-tinged fluid under pressure. The colloidal gold test was negative.



Roentgen examination of the skull revealed an enlarged sella turcica and eroded clinoid processes. The frontal sinuses were very large and protuberant.

*Course.* The patient never regained consciousness. He became cyanotic and died nine hours after admission.

*Necropsy Findings* (Restricted to examination of the skull only). The body was that of a muscular white male. The left side of the mouth showed a slight drooping. The mucosa of the lips and finger nails were cyanotic. The pupils were round and the right was slightly larger than the left. The teeth were in good condition. The head appeared much larger than normal, and the cheek bones and jaw were very prominent. The nose also was large. The skin of the face was deeply pigmented and cyanotic.

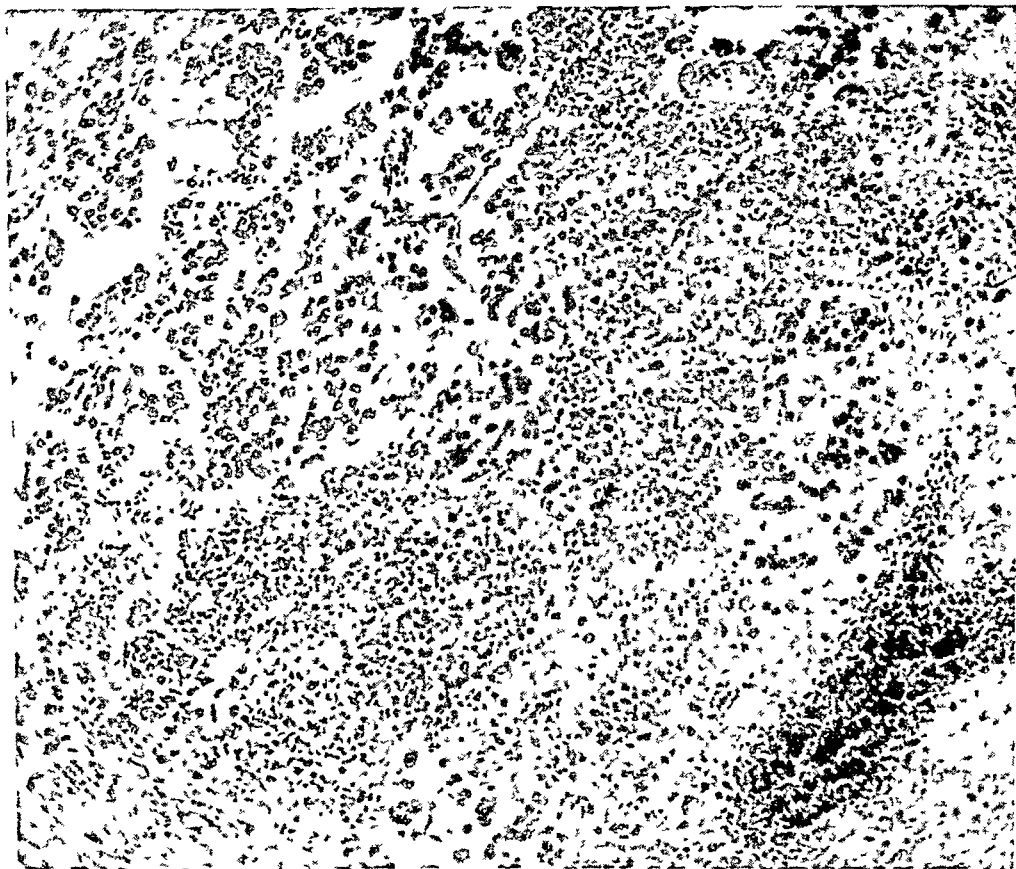


FIG. 2. Section from the surface of the tumor showing areas of necrosis and hemorrhage.

*Extremities.* The arms extended down to the middle third of the thigh. The fingers were short, very broad (up to 3 cm. in diameter), and the ends were rounded. The middle fingers was 8 cm. long. The legs were short but very muscular.

*Brain.* The brain weighed 2,640 grams. The consistency was soft, and the convolutions were prominent. Between the meninges there was a recent bloody exudate.

*Hypophysis.* The hypophysis was transformed into a nodular tumor mass measuring 50 by 35 by 25 mm. It was soft and the surface was discolored purple red. On the anterior aspect there was a cavity 25 mm. in diameter filled with blood. The stalk measured 15 mm. in length and 7 mm. in diameter. The blood vessels at the base of the brain were thin-walled and patent.

The sella turcica was markedly enlarged, eroded, and measured 28 mm. in anterior-posterior diameter, 35 mm. in transverse diameter, and 20 mm. in depth.

*Microscopic Description.* The tumor of the hypophysis occupied the anterior lobe and was composed of small polygonal-like cells with an ample eosinophilic staining cytoplasm. The nuclei were small, oval to round, and only rarely irregular in size. The cells formed acini which often anastomosed with one another. The stroma of the tumor was loose and frequently contained dilated and congested blood spaces. In some places the tumor cells contained irregular and hyperchromatic nuclei. Other parts of the tumor showed marked regressive changes and contained large areas of extravasated red blood cells and focal areas of necrosis. The tumor was surrounded by a thickened fibrillar capsule which contained numerous dilated blood spaces packed with red blood cells. There were no evidences of malignancy.

*Anatomical Diagnoses:* (1) Eosinophilic adenoma of the anterior lobe of the hypophysis. (2) Subarachnoid hemorrhage due to necrosis of the tumor. (3) Marked enlargement of the sella turcica. (4) Acromegaly (clinically).

#### COMMENT

Subarachnoid hemorrhage as a complication of an eosinophilic adenoma is most unusual. In reviewing the literature a case similar to ours, in which the tumor produced a subarachnoid hemorrhage, has not been found. Bailey<sup>4</sup> does refer to the possibility of the pituitary tumor in acromegaly in its terminal stages of undergoing such changes as degeneration or hemorrhage. Our case is of particular interest in that the tumor leaked blood into the subarachnoid space and clinically suggested the diagnosis of meningitis which was subsequently changed to subarachnoid hemorrhage following spinal puncture.

In a series of eight cases of eosinophilic adenoma of the hypophysis encountered at the Cook County Hospital, Chicago, taken from the files of 12,450 consecutive autopsies, only two manifested the clinical picture of acromegaly. Both cases were males, aged 53 and 74 years. The cause of death in the first case was postoperative pneumonia following a thyroidectomy for a toxic goiter, and in the second case death was due to diabetic gangrene. In both cases the tumor had broken through the capsule; however, histologically the cells appeared regular and orderly.

Acromegaly is usually a chronic progressive disease developing after the age of 20. Its presence may be noted for many years. In spite of the large size of these tumors, sufficient normal tissue is frequently present to carry on most of the normal functions of the pituitary gland.

Eosinophilic adenomas of the pituitary gland are usually soft, nodular, and may show degenerative changes with foci of necrosis and hemorrhage. The tumor may vary in size from a few millimeters to six centimeters in diameter. As the tumor grows larger it may become invasive and thus act as a malignant neoplasm, although histologically the cells lining the acini are orderly with regular oval nuclei and an eosinophilic staining cytoplasm.

Tumors of the anterior lobe of the hypophysis in which the eosinophilic cells predominate manifest clinical symptoms by mechanical pressure of the enlarged tumor on surrounding structures or by perverted activity of the altered anatomical-physiology of the gland. Therefore, such symptoms as blindness, diabetes, impotence, obesity, amenorrhea, sterility, or cryptorchism may occur. The bone changes are usually restricted to the skull and extremities. There is an overgrowth of the bones causing the typical prognathism of the jaw, and an

increase of the size of the hands. Roentgen examination may show proliferative changes of the tips of the fingers described as "tufting." The widening of the sella turcica seen on roentgenogram is fairly common.

Increased metabolic rate is frequently noted in acromegaly and its presence should not be confused with a toxic goiter. The visual disturbances are due to pressure of the tumor upon the optic chiasm, and bitemporal hemianopsia may be noted.

#### SUMMARY

A case of an eosinophilic adenoma of the hypophysis causing a subarachnoid hemorrhage is described.

The patient was a 35 year old male with clinical features of acromegaly.

The tumor had widened and eroded the sella turcica, and had undergone degenerative changes such as necrosis and hemorrhage. Histologically the tumor was benign.

The clinical picture of intracranial pressure was manifested by headaches, vomiting, rigidity of the neck, stupor and coma.

#### BIBLIOGRAPHY

1. MINKOWSKI, O.: Arch. exper. Path. u. Pharmacol., 1893, xxxi, 85.
2. CUSHING, H.: The pituitary body and its diseases, 1912, J. B. Lippincott Co., Philadelphia.
3. LEVY, S. S.: Hyperpituitarism, Brit. Med. Jr., 1936, 931, 3935.
4. BAILEY, P.: Intra-cranial tumors, 1933, Charles C. Thomas, Springfield, Illinois.

---

### KLEBSIELLA MENINGITIS: A CASE CURED WITH STREPTOMYCIN \*

By EUGENE M. SCHLOSS, Major, M.C., JAY H. DAVIDSON, Captain, M.C., and KATHLYN C. HILTON, 2nd Lt., W.A.C. (SnC), *Phoenixville, Penna.*

ALTHOUGH Friedländer's bacillus (*Klebsiella pneumoniae*) has been known to attack any system of the body,<sup>1, 2</sup> either as the sole agent of disease or as an etiological *particeps criminis*, it has been found to produce meningitis with comparative infrequency. Ransmeier and Major<sup>3</sup> reviewed the literature in 1942 and found but 29 reported cases, to which they added one of their own; Mori<sup>4</sup> reported a single case in 1943; King,<sup>5</sup> bringing the review up to date in February, 1946, commented on the reports of two additional cases not formally presented and described the process in a case which he had encountered. Thus, there would appear to be a total of 32 reported cases, plus two to which reference has been made on the basis of personal communications,<sup>6, 7</sup> in all of which the high mortality prior to the recent use of antibiotic medication has been a striking feature.

The situation was well summarized by Ransmeier and Major, who wrote that "a few patients with meningitis due to Friedländer's bacillus have recovered after administration of sulfapyridine or sulfadiazine, while formerly the condition was almost certainly fatal." Of the instances in which sulfonamides have been em-

\* Received for publication September 19, 1946.

From the Medical Service of the Valley Forge General Hospital, Phoenixville, Pennsylvania.

ployed, there have been two cures attributed to sulfapyridine<sup>8, 9</sup> and one death,<sup>10</sup> one death in a case treated with sulfanilamide,<sup>3</sup> two cures and one death in cases treated with sulfadiazine,<sup>5, 6, 7</sup> and one recovery reported after the use of "Soluseptazine."<sup>4</sup>

Of present-day antibiotic agents in wide usage, there would appear to be justification for the clinical use of either the sulfonamides, particularly sulfadiazine, or the more recently developed streptomycin. Penicillin has been found wholly ineffective against *Klebsiella pneumoniae* in vitro<sup>11</sup> and hence no encouragement is offered for its employment in vivo. On the other hand, both sulfadiazine<sup>12</sup> and streptomycin<sup>13</sup> have demonstrated a high degree of inhibition against Friedländer's bacillus in vitro and a considerable therapeutic value on clinical application. The striking progress made possible by the recent use of sulfonamides in *Klebsiella meningitis* has already been commented upon. Herrell and Nichols<sup>14</sup> have reported very favorably on the use of streptomycin in chronic pulmonary suppurative disease and somewhat so on its application in *Klebsiella ozena*, aside from its known value in Friedländer's bacillus pneumonitis, for which its use has recently received official authorization.<sup>15</sup>

It was in this status of knowledge concerning the disease and its therapy that a patient with *Klebsiella meningitis* was recently hospitalized at the Valley Forge General Hospital.

#### CASE REPORT

A white male, 21 years of age, had been wounded in Germany on April 14, 1945, by a shell fragment which had entered the left upper face and had emerged through the palatal bone, causing extensive damage to the left cheek, orbit, maxillary antrum, nasal septum and ethmoid cells. This resulted in a naso-orbital fistula for which surgical closure was completed and plastic repair begun. On February 1, 1946 he abruptly developed a generalized convulsion, followed by stupor; he became febrile and exhibited slight nuchal rigidity and an equivocal Kernig's sign. Spinal tap disclosed cloudy fluid under increased pressure, and smears showed a gram-positive diplococcus which, on culture, proved to be pneumococcus, type VI; the same organism was obtained on blood culture. He was treated with penicillin intramuscularly and intrathecally, and sulfadiazine intravenously, and, after a very stormy two weeks, went on to ultimate recovery in all respects in six weeks. It was decided to send the patient on a 90-day convalescent furlough at the conclusion of which further plastic repair of the left orbital deformity would be undertaken.

However, about May 14, 1946, while on furlough, the patient developed an upper respiratory infection, manifested by rhinorrhea, which went on to a purulent nasal discharge with intermittent nasal obstruction. On May 27, 1946 he began to have headache, malaise and fever, and the following day was returned to this hospital in a state of some mental confusion. On admission he was found to be febrile and lethargic, had a temperature of 100° F. orally and a pulse rate of 94 per minute, and exhibited slight nuchal rigidity; the leukocyte count was 27,000, with a differential count of 91 polymorphonuclears and 9 lymphocytes. In view of the past history, the medical officer of the day felt that, in all probability, this represented a recurrence of the pneumococcal meningitis and immediately started treatment with penicillin, 30,000 units every three hours, plus sulfadiazine, 5 gm. intravenously. When lumbar puncture was performed the following morning, the spinal fluid was found to be grossly cloudy but, because of the patient's hyperexcitability, no pressure reading could be made; after drainage of 10 c.c. of fluid, 20,000 units of penicillin were instilled intrathecally. This specimen of fluid showed a count of 9,000 leukocytes,

of which 85 per cent were polymorphonuclears; sugar was 53 mg. per cent, Pandy test 4 plus, and total protein was 415 mg. per cent; smears revealed many pus cells but no organisms; culture, reported later, disclosed *Klebsiella pneumoniae*. The patient continued to run a severe toxic course with temperature elevations spiking to 104° F., and, later the same day, penicillin was increased to 200,000 units every three hours; this change was predicated on our experience with an earlier case of pneumococcic meningitis with a resistant focus (to be reported later). During the next 24 hours the patient became comatose; temperature ranged from 102° to 105° F. (rectal); pulse rate varied from 105 to 130 per minute, respirations from 30 to 48 per minute, shallow and irregular. The absence of any clinical response to medication became obvious. Lumbar puncture was repeated and the spinal fluid pressure was read at 290 mm.; 10 c.c. of cloudy fluid were withdrawn and, again, 20,000 units of penicillin instilled. Culture of this fluid also showed *Klebsiella pneumoniae*, even after the massive dosage of penicillin administered intramuscularly and the instillation of 20,000 units intrathecally, and the continued use of sulfadiazine intravenously. Blood sulfadiazine level after the first infusion was 7.6 mg. per cent, but no subsequent determinations were made because of the condition of the patient's veins.

About four hours after the second spinal tap, the laboratory reported that *Klebsiella* had been isolated in pure culture from fluid drawn at the first tap. The patient then appeared to be in extremis, and it was decided to discontinue both penicillin and sulfadiazine, and to institute streptomycin therapy immediately. Accordingly, the patient was given one million units (1.0 gm.) intramuscularly and the spinal puncture was repeated; 100,000 units of streptomycin dissolved in 10 c.c. of spinal fluid were instilled intrathecally. Thereafter, 500,000 units of streptomycin were injected intramuscularly every three hours, and 50,000 units were given intrathecally every 12 hours. During the next 48 hours, the patient remained critically ill and the temperature fluctuated between 101° and 106° F. (rectal). Spinal fluid remained grossly cloudy and pressure continued above normal levels. Smears made from the first spinal fluid obtained after the original intrathecal injection of streptomycin (12 hours) disclosed encapsulated gram-negative bacilli in profusion, but cultures were negative then and thereafter; the inference was drawn that the organisms seen on smear were already killed but not disintegrated, certainly no longer viable or capable of reproduction. Smears during the next 24 hours showed decreasing numbers of such organisms, and cultures remained sterile. Thereafter, both smears and cultures were negative. Toward the end of the 48-hour period, the patient roused occasionally and took some fluid before again lapsing into coma, and fluid-electrolyte level was maintained intravenously. When, however, it was found that there was no appreciable improvement in temperature or nuchal rigidity, the possibility of continued central nervous system irritation from the intrathecally administered streptomycin was considered, and this avenue of therapy was discontinued. The use of 500,000 units intramuscularly every three hours was maintained over a period of 14 days. Within 12 to 18 hours after discontinuance of streptomycin intrathecally, the clinical status of the patient improved to a point where he was rational and asked for food and water; the temperature dropped to 100.2° F. (rectal); while headache disappeared, the patient continued to complain of "pains all over the body," an effect not unusual during the administration of streptomycin. Thereafter, he continued to improve, the temperature reaching 102° F. the following day, 101° F. during the next 24 hours, and seldom rising to 99.6° F. (orally) after the sixth day of the current illness. It was normal after the fourteenth day. Nuchal rigidity and cloudiness of the spinal fluid cleared progressively, and when last observed, more than two weeks after cessation of all therapy, the patient could be considered cured of the *Klebsiella* meningitis. Spinal fluid on June 28, 1946 was entirely normal from the standpoint of pressure and appearance, cell count, sugar, protein content, smear and culture, and there were no residual clinical signs of the disease.

## DISCUSSION

In the case described, both penicillin, in massive doses, and sulfadiazine, in moderate amounts, were used without any appreciable improvement over a period of about 36 hours, at the end of which time spinal fluid culture still showed a heavy growth of *Klebsiella pneumoniae*. Twelve hours after beginning therapy with streptomycin, the spinal fluid was sterile and remained so thereafter. During the first 48 hours of streptomycin administration, the patient underwent some improvement in that he roused from coma from time to time and became capable of taking small amounts of liquids orally; however, true emergence from stupor, drop in temperature, and subsidence of nuchal rigidity did not occur until 12 to 18 hours after discontinuance of the intrathecal mode of administration. It was our impression at the time that the continued fever and rigidity were due to chemical irritation of the central nervous system by the streptomycin, although Anderson and Jewell<sup>16</sup> had administered it in amounts up to 20,000 units intrathecally without meningeal irritation in a case of tuberculous meningitis. It has been demonstrated by Zintel et al.<sup>17</sup> that comparatively little streptomycin appears in the spinal fluid following considerable intramuscular dosage in the absence of cerebrospinal disease, whereas a substantial amount is demonstrable in the presence of diffuse meningeal inflammation; they cite one instance in which the spinal fluid level of streptomycin in a case of *H. influenzae* meningitis reached 25 units per c.c. after administration of one million units in 24 hours. Our rationale, therefore, in the use of large amounts intrathecally is open to question unless one considers that this patient was apparently in extremis at the time that streptomycin was first instituted, and it was felt that only heroic measures could turn the tide of disease.

It is unfortunate that we had no method of estimating the blood or spinal fluid levels of streptomycin at this installation. However, susceptibility studies made on cultures from this case would seem to justify our use both of streptomycin and of the massive doses employed. Sensitivity tests to streptomycin, penicillin and sulfadiazine were run, using modified methods. For the penicillin and streptomycin, serial dilutions of the drugs were made in cold sterile physiological saline, starting with a concentration of 200 units per c.c. and ending with a concentration of 0.39 unit per c.c. To each tube 3.5 c.c. cold sterile brain-heart infusion broth (Difco) were added and 0.5 c.c. saline suspension of 300 million bacteria per c.c. An 18-hour growth of the test organism on an agar slant was suspended in saline and standardized to 300 million bacteria per c.c. on the Coleman Junior Spectrophotometer at 420 millimicrons. Thus the final concentrations of the drugs ranged from 40 units per c.c. in the first tube to 0.078 unit per c.c. in the tenth tube. The series was incubated 18 hours at 37° C. and the last tube showing complete inhibition of growth was taken as the end-point.

In the case of sulfadiazine, serial dilutions of the sodium salt were made in 0.01 N NaOH, beginning with a solution containing 500 mg. per 100 c.c. and ending with a solution containing 31.25 mg. per 100 c.c. To each tube 3.5 c.c. of brain-heart infusion broth and 0.5 c.c. of a saline suspension of bacteria standardized to 300 million per c.c. were added. Thus the final concentrations of the drug were 100 mg. per 100 c.c. in the first tube and 6.25 mg. per 100 c.c. in the fifth tube. The series was incubated and read as above.

In all series a control tube containing 1 c.c. of the final dilution of the drug

and 4 c.c. of brain-heart infusion broth was included to check the sterility of the components of the test.

The results showed the *Klebsiella pneumoniae* to be sensitive to 20 units per c.c. of streptomycin but not to 10 units per c.c., and not sensitive to 40 units per c.c. of penicillin or to 100 mg. per 100 c.c. of sulfadiazine. Thus, in view of the almost invariably fatal outcome of *Klebsiella* meningitis prior to the use of sulfonamides and the resistance of this particular organism to penicillin and sulfadiazine, it would appear that this patient's recovery was effected best by the administration of streptomycin. It is noteworthy also that a concentration of 20 units per c.c. of streptomycin was necessary for inhibition of the organism in vitro; the implication is obvious that high concentrations of the drug would, therefore, be required for clinical effectiveness.

### SUMMARY

A case of *Klebsiella meningitis* is reported in which streptomycin was employed intramuscularly, 500,000 units every three hours for 14 days and intrathecally with an initial dose of 100,000 units and 50,000 units every 12 hours for three additional doses; total, 56,250,000 units or 56.25 gm. The patient made a complete recovery.

### BIBLIOGRAPHY

1. BAEHR, G., SCHWARTZMAN, G., and GREENSPAN, E. B.: *Bacillus Friedländer* infections, Ann. Int. Med., 1937, x, 1788.
2. SWARTZ, E. P., and ROHDE, P. A.: *Klebsiella* (Friedländer's bacillus) infections in an Army hospital, Am. Jr. Clin. Path., 1946, xvi, 88.
3. RANSMEIER, J. C., and MAJOR, J. W.: Friedländer's bacillus septicemia and meningitis, Arch. Int. Med., 1943, lxxii, 319-328.
4. MORI, G. E.: Meningitis due to Friedländer's pneumobacillus in child 26 months old, An. d. Hosp. Ninos e Inst. Puericult. de Rosario., 1943, 187-196.
5. KING, SAMUEL J.: Friedländer's bacillus meningitis with report of case treated unsuccessfully with sulfadiazine, Ann. Int. Med., 1946, xxiv, 272.
6. NELSON, R. A., and LONG, P. H.: The clinical use of sulfadiazine in the therapy of bacterial infections other than pneumonia, Bull. Johns Hopkins Hosp., 1941, lxi, 303.
7. JULIANELLE, L. A.: Personal communication as listed by Ransmeier and Major.
8. MONTES, G. G., and REAL, W. A.: Meningitis purulenta a neumobacilo de Friedländer (*Klebsiella pneumoniae*) curado con dagenan, Bol. Soc. cubana de pediat., 1940, xii, 5.
9. ROBERSTON, C. W.: Meningitis due to *B. Friedländer*: Recovery of a case treated with sulfapyridine, Canadian Med. Assoc. Jr., 1941, xlv, 70.
10. KOLMER, J. A., and RULE, A. M.: Sulfanilamide and sulfapyridine in the treatment of *B. Friedländer* (*Klebsiella pneumoniae*) infections of mice, Proc. Soc. Exper. Biol. and Med., 1939, xlii, 305.
11. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Activity of penicillin in vitro, Proc. Soc. Exper. Biol. and Med., 1942, 1, 277.
12. FEINSTONE, W. H., WILLIAMS, R. D., WOLFF, M. S., HUNTINGTON, E., and CROSSLEY, N. L.: The toxicity, absorption and chemotherapeutic activity of 2-sulfanilamide-pyrimidine (sulfadiazine), Bull. Johns Hopkins Hosp., 1940, lxxvii, 427.
13. HEILMAN, F. R.: Streptomycin in the treatment of experimental infection with microorganisms of the Friedländer group (*Klebsiella*), Proc. Staff Meet., Mayo Clin., 1945, xx, 33.

14. HERRELL, W. E., and NICHOLS, D. R.: The clinical use of streptomycin: A study of 45 cases, *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 449.
15. KEEFER, CHESTER S.: Official statement concerning streptomycin, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 31.
16. ANDERSON, D. G., and JEWELL, M.: The absorption, excretion and toxicity of streptomycin in man, *New England Jr. Med.*, 1945, ccxxxviii, 485.
17. ZINTEL, H. A., FLIPPIN, H. F., NICHOLS, A. C., WILEY, M. M., and RHOADS, J. E.: Studies on streptomycin in man. Absorption, distribution, excretion and toxicity, *Am. Jr. Med. Sci.*, 1945, ccx, 421.

---

## ESSENTIAL THROMBOPHILIA: REPORT OF A CASE\*

By JOSEPH A. EPSTEIN,† M.D., *New York, N. Y.*, and  
ISAAC H. RICHTER, M.D., *Brooklyn, N. Y.*

IN this communication we wish to present a case which clinically and pathologically conforms to the disease entity known as "Essential Thrombophilia." In 1937, Nygaard and Brown defined this syndrome and reported five cases in which thrombosis occurred in the vessels of the extremities and in the brain, kidney and heart. The thrombosis occurred without any previously known disease of the vessels involved such as is seen in thromboangiitis obliterans and in arteriosclerosis. The pathological changes in the vessels were minimal and of a non-reacting type. Thrombosis was evident without signs of disease in the intima and in the other coats of the vessel. In two cases a slight cellular reaction in the media and adventitia was seen. The occluding thrombus was not organized. There were infarcts found in the lungs, kidney and spleen.

The major pathological process appeared to involve the stability of the suspension of blood platelets rather than specific disease of the vessel walls. An increased coagulability of the blood plasma and an alteration in the distribution of the serum proteins coincided with the periods of thrombus formation. These findings were not considered to be specific for the disease although they were present in four of the five cases reported. The elevation in the platelet count was considered significant. In two cases the marked increase in the globulin-fibrinogen fraction of the serum proteins was believed to be the factor favoring thrombus formation by reducing the suspension stability of the platelets. In reviewing the literature we noted that Nygaard and Brown were the only ones who reported this syndrome. Because of this we feel that it would be of interest to report the following case.

### CASE REPORT

C. K., a 30 year old woman, was admitted to the Medical Service of Dr. A. Louria of the Jewish Hospital of Brooklyn on July 27, 1946 complaining of shortness of breath and continuous pain and swelling of her right lower extremity of three weeks' duration. Her symptoms increased in severity. Three days prior to admission, a bluish discoloration of the skin on the dorsum of her right foot was noted. That day, she complained of pain over the left posterior aspect of her chest.

\* Received for publication November 1, 1946.

From the Department of Pathology and the Peripheral Vascular Clinic of the Jewish Hospital of Brooklyn.

† Assistant Resident in Surgery.



Since September, 1945 she had noticed dyspnea on moderate exertion and intermittent swelling of her legs. She had been bedridden since June 11, 1946 and was given digitalis and ammonium chloride for relief.

Her past history revealed repeated attacks of chorea from the ages of 11 to 18. At the age of 23 she had three febrile episodes diagnosed as acute rheumatic fever. The patient did not smoke.

Physical examination revealed an acutely ill, obese white woman. She was cyanotic, dyspneic and orthopneic. Her hair was gray, and she appeared to be much older than her stated age. She was alert and coöperative. Her temperature was 103° F., pulse 112, and respirations were 32. Her blood pressure was 128 mm. Hg systolic and 80 mm. diastolic.

Examination of her thorax revealed diminished to absent resonance over the left base posteriorly. Vocal fremitus was decreased and fine crepitant râles were heard both anteriorly and posteriorly. Her heart was not enlarged. Systolic murmurs were noted over both mitral and aortic regions. Her abdomen was pendulous and her right lower extremity was markedly edematous. The skin down to the ankle was warm and hyperemic. Below the ankle, this area was sharply demarcated from a cold, intensely cyanotic foot. The pulsations of the femoral artery were present bilaterally. Pulsations of the popliteal artery and the more peripheral vessels were absent on the right.

Oscillometric readings taken on July 27, 1946 revealed no oscillations at the right knee and ankle. On the left, the readings were 3.5 at the knee and 1.5 at the ankle. On July 28, 1946 large vesicles filled with thin, yellow fluid were noted on the dorsum of the right foot. Splanchnic and paravertebral blocks using 1.5 per cent metycaine were performed at L.1 to L.4. Following injection, there was symptomatic relief and a noticeable lightening of the mottled areas of skin which had developed above the ankle. There was a recession in the intensity of the cyanosis of the foot. On July 31, 1946 her temperature rose to 106° F., and she was irrational. Sensation in her toes was absent. The skin was black and dry up to the metacarpophalangeal joints. She died the following day after her temperature rose to 108° F. Her respirations were noted to be irregular and spasmodic before death. She had received penicillin and papaverine since admission.

Examination of the urine was negative. Blood study on July 28, 1946 revealed a hemoglobin of 55 per cent with 3,340,000 red blood cells and 20,950 white blood cells. Of these, 83 per cent were polymorphonuclear leukocytes, 4 per cent were band forms, 9 per cent were lymphocytes and 4 per cent were monocytes. Eight normoblasts were counted. Poikilocytosis, anisocytosis, polychromatophilia and achromia were evident. The Klein reaction was negative. Blood sugar was 112 mg. per cent, urea nitrogen 33.4 mg. per cent, total protein 6.10 per cent, albumin 3.37 per cent, and globulin 2.73 per cent. The A/G ratio was 1.2.

The blood cultures were sterile.

Skin temperatures taken on July 31, 1946 revealed values of 79°–80° F. over the toes and dorsum of the foot on the right as compared to values of 90°–90.5° F. on the left. The calf temperatures were 91° F. on the right and 93° F. on the left.

During the two days preceding death, the temperature, pulse and respirations rose steadily.

The clinical diagnosis was phlebothrombosis and thrombophlebitis of the right lower extremity; embolus, right popliteal artery; bronchopneumonia, left lower lobe; rheumatic heart disease and obesity. Thromboangiitis obliterans, although rare in females, was also mentioned as a possible diagnosis.

*Necropsy. Gross findings:* The postmortem examination revealed a massive pitting edema of the entire right lower extremity. The skin of the foot up to the malleoli was purple-red and gray and contained several collapsed bullae. The toes were blue-black, dry and wrinkled.

The heart weighed 380 grams. There was a large amount of subepicardial fat and fatty infiltration of the right ventricular wall was evident. The valves were grossly normal. There was no evidence of rheumatic heart disease and no mural thrombi.

A large, twisted yellow and red-purple embolus was removed from the pulmonary arteries. There were multiple old and fresh infarcts in the left lower lobe of the lungs. Both lower lobes were extremely congested.

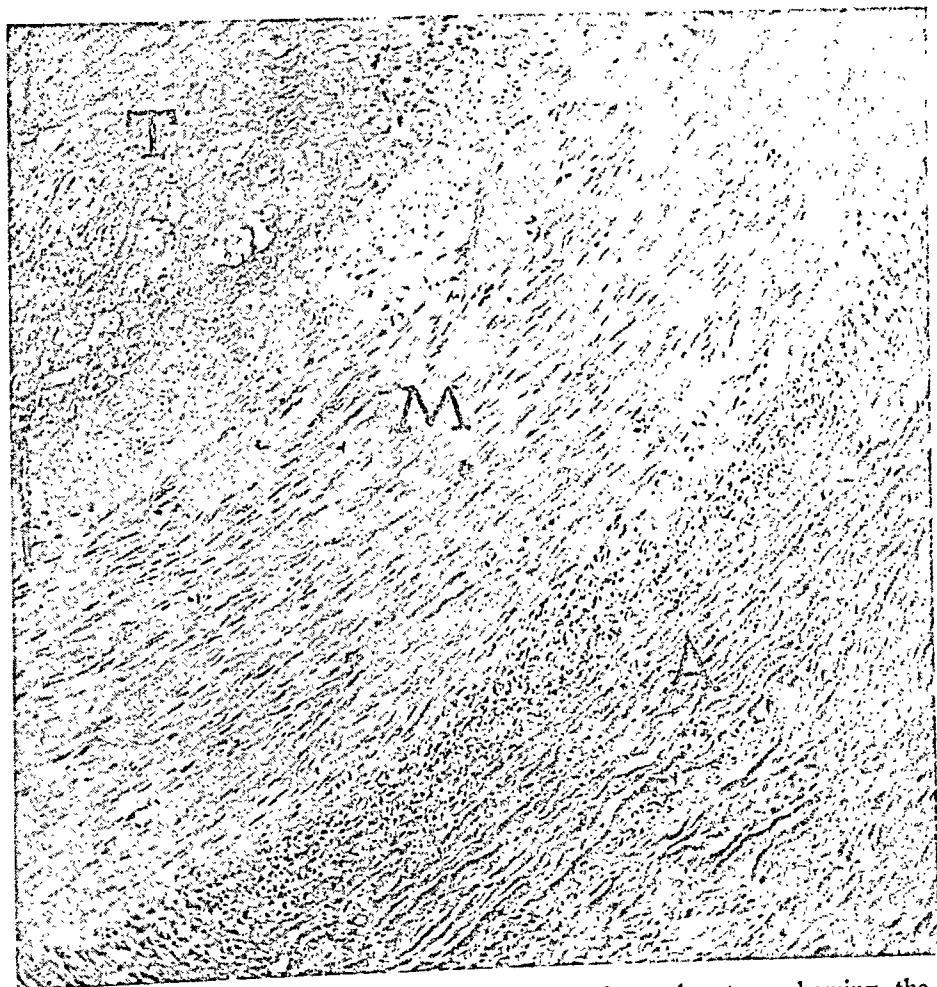


FIG. 1. Section taken through the walls of the femoral artery showing the bland thrombus, T, the media, M, and the adventitia, A. The collection of round cells in the central layers of the adventitia is well demonstrated. Hematoxylin and eosin.  $\times 35$ .

The spleen weighed 480 grams and was extremely friable. It contained large old and recent infarcts. The splenic artery in its entire length was occluded by a firm, yellow, gray and red thrombus. The splenic vein at the hilus was filled with a soft red-purple clot. Along the posterior inferior surface of the pancreas, the vein contained an old organized and well canalized thrombus.

The right femoral artery was occluded by a pink and yellow thrombus that extended peripherally into the popliteal vessels. The right iliac, femoral and popliteal veins were distended with a red-purple, soft, friable thrombus that in part was adherent to the intimal surface. There was no evidence of fibrosis or tissue reaction about the neurovascular bundle.

*Microscopic findings:* The femoral artery was occluded with a thrombus composed of hyalinized platelets, fibrin and red blood cells. There were early signs of organization at the periphery of the thrombus. The media showed a normal arrangement of its fibers. Immediately peripheral to the fibers of the media was a zone of partially fragmented acidophilic collagenous tissue. In the interstices there were



FIG. 2. High magnification of the zone of adventitia immediately adjacent to the media showing the cellular infiltration.  $\times 600$ .

scattered small and large reticulated nuclei resembling fibroblasts. Similar cells were seen in smaller numbers about the vasa vasorum (figures 1, 2). A small calcific plaque was seen in the media beneath a slightly thickened intima. The femoral vein showed a similar and less prominent type of infiltration.

In a preparation from the popliteal artery an identical zone of partially fragmented collagenous tissue with interspersed round cells was noted. The intima was moderately thickened. Among the fibers of the media and adventitia of the popliteal

vein, occasional lymphocytes and plasma cells were evident. No unusual reaction was observed about the tibial nerve.

In a preparation from the splenic artery, the thrombus showed no evidence of organization. Signs of intimal reaction were absent. The cellular infiltration of the adventitia was similar to that in the femoral vessel. The splenic vein contained a thrombus of the bland type described above. Scattered among the fibers of the media and adventitia were the chronic inflammatory cells already noted.

### DISCUSSION

In this case there was no history of trauma, no evidence of acute infection, and no pathological changes in the heart to account for the widespread thrombosis involving the vessels of the right lower extremity, spleen and pancreas. Microscopic examination revealed the minimal tissue reaction described by Nygaard and Brown as characteristic of essential thrombophilia. Unfortunately, platelet counts and studies of plasma coagulability were not made. The plasma proteins, however, showed the increase in the globulin fraction described by these authors in their report.

### SUMMARY

We are presenting a case in which multiple thrombi occurred in vessels of the right lower extremity, the spleen and pancreas in a 30 year old woman. The history and microscopic findings were characteristic of the syndrome called "essential thrombophilia" as described by Nygaard and Brown.

### BIBLIOGRAPHY

1. NYGAARD, K. K., and BROWN, G. E.: Essential thrombophilia. Report of five cases, Arch. Int. Med., 1937, lix, 82-106.

---

## IDIOPATHIC STEATORRHEA: WITH REPORT OF A CASE OF WHIPPLE'S DISEASE\*

By HENRY A. CHAPNICK, M.D., *Detroit, Michigan*

THAT diarrhea is not infrequently associated with diseases in organs other than the colon has been appreciated for a long time. Thus, diarrhea in hyperthyroidism and occasionally in diabetes<sup>1</sup> and in Addison's disease is well known. Of greater pertinence is the frequency of diarrhea or steatorrhea in such deficiency diseases as sprue, pellagra, and pernicious anemia. In recent years some evidence has been presented pointing towards the identity of sprue, tropical or non-tropical, celiac disease, and idiopathic diarrhea. This view is epitomized in Hane's<sup>2,3</sup> statement that celiac disease is to sprue as cretinism is to myxedema.

Disturbing to this unitarian view has been the lack of uniform pathological findings. Thayssen<sup>4</sup> in discussing the pathological findings in sprue emphasizes the inconstancy of small bowel atrophy in that disease. The very name "sprue-like syndrome" suggests that a variety of pathological lesions is grouped together because of a similar clinical course.

\* Received for publication November 4, 1946.

Although steatorrhea is a *sine qua non* for the diagnosis of sprue, other diseases than sprue may have steatorrhea. Bargaen and his associates<sup>5</sup> have emphasized the lack of pancreatic enzymes as a cause of steatorrhea, and have demonstrated the diagnostic importance of determining the enzyme content of duodenal juice. Fibrocystic disease of the pancreas in children similarly may be distinguished by a diminution of pancreatic enzyme. Of particular interest is the manifestation of steatorrhea in Hodgkin's disease of the mesenteric glands as described by Fairley and Mackie.<sup>6</sup> Tuberculous mesenteric adenitis<sup>7</sup> and jejunoileitis<sup>8</sup> have also been observed to produce a sprue-like syndrome. In an excellent study by Miller and Barker<sup>9</sup> of 33 patients with the sprue syndrome who responded to an antisprue régime, two died after six and 21 months respectively. One of these patients was found to have tuberculous peritonitis, and the other carcinoma of the pancreas.

In recent years, Whipple's disease<sup>10</sup> or lipophagic intestinal granulomatosis has aroused some interest. The classical syndrome as described by Whipple consists of steatorrhea, arthritis, anemia, emaciation, an enlarged abdomen, and skin pigmentation. Pathologically, in addition to panserositis, there are enlarged intestinal villi filled with lipids, and enlarged mesenteric nodes showing dilated sinuses giving both the lymph nodes and the villi a swiss-cheese pattern. To date 17<sup>10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23</sup> cases fulfilling the above general criteria have been described, though some of these lack such important symptoms as diarrhea, steatorrhea, or arthritis. Although all the cases described showed mesenteric adenopathy, not all presented the classically described dilated villi.

Only one case<sup>21</sup> has so far been reported ante mortem and that was following an exploratory laparotomy. The antemortem diagnoses of Hodgkin's disease, ulcerative colitis, Boeck's sarcoid, and leukemia were not infrequently entertained, and reflect the diagnostic difficulties. While all cases reported have shown a varying degree of anemia, one case had an antemortem diagnosis of lymphatic leukemia, and another a diagnosis of lymphatic leukemia and hemolytic icterus for which a splenectomy was done.

Captain Marcell Patterson, Medical Corps, then on our service, was the first to suggest that our patient might have lipophagic intestinal granulomatosis after comparing the clinical picture with that of a recently reported case.<sup>22</sup>

#### CASE REPORT

A 37 year old white soldier, stationed in Italy, was well until August 1944 when he began complaining of weakness and frequent bowel movements. These bowel movements occurred mostly during the morning hours; borborygmi and tenesmus were present most of the time. There was no melena; the stools were usually watery, at times soft and occasionally formed. The patient's best weight was 130 pounds; when he returned to the United States in October 1944 it had decreased to 100 pounds. On one occasion his liver was considered to be slightly enlarged. Repeated stool examinations were negative for parasites, ova and occult blood. In March 1945 gastrointestinal roentgenographic studies revealed the stomach and duodenum to be normal except for the presence of hypermotility and an atypical pattern of the small bowel. Roentgen studies following a barium enema were reported as normal. In June 1945 a peritoneoscopy was done, and "yellowish plaques" were described on the liver. These plaques were seen at a subsequent laparotomy at which time a biopsy of the liver and of the mesenteric nodes was taken. Microscopic examination of this biopsy was interpreted as "a subacute inflammatory reaction involving the liver and Glisson's capsule." Unfortunately this tissue was not available for review.

The patient was transferred to Percy Jones General Hospital in October 1945 with a formal diagnosis of cirrhosis of the liver. That the formal diagnosis was only an administrative label was obvious from the other diagnoses entertained, such as schistosomiasis, histoplasmosis, and leishmaniasis. His complaints were essentially as given above. The patient gave no history of arthritis.

TABLE I

Date	R.B.C. (In millions)	W.B.C	Hb. %	Neutro- philes	Lympho- cytes	Eosino- philes	Baso- philes	Mono- cytes	Sedi- menta- tion Rate
Oct. 5, 1944	3.82	6150	70	78	16	4	2		57
Oct. 31, 1945	4.16	7750	66	76	20	1		3	37
Nov. 15, 1945	3.01	3700	55	75	25				
Dec. 3, 1945	2.94	6800	58	81	19				15
Dec. 13, 1945	3.2	4200	54	78	18			4	13

*Examination.* The patient was a markedly emaciated man with a dry, sallow, yellowish skin. There was no icterus. His weight was 80 pounds. The tongue showed slight atrophy. The heart and lungs were essentially negative. There were thrombosed veins in both arms from intravenous administration of blood, glucose and



FIG. 1. Gross appearance of the liver and spleen showing the shaggy exudate over the liver and spleen capsules.

plasma. The blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. There was no abdominal tenderness. The liver, spleen, and kidneys were not palpable. There was no evidence of ascites. There were no enlarged abdominal veins. The

muscles showed marked atrophy. Reflexes were normal. There was minimal edema of both legs.

*Laboratory Findings.* Blood counts were as shown in table 1. Urine examination showed an occasional trace of albumin, with a specific gravity of 1.019, and no sugar; microscopic examination was negative. The non-protein nitrogen was 29 mg. per cent, cholesterol 66 mg. per cent; cholesterol esters 38 mg. per cent; total proteins 4 grams per cent, albumin 2.7 grams per cent; globulin 1.3 grams per cent; A/G ratio 1.5:1; calcium 8.7 mg. per cent; phosphorus 2.8 mg. per cent; alkaline phos-

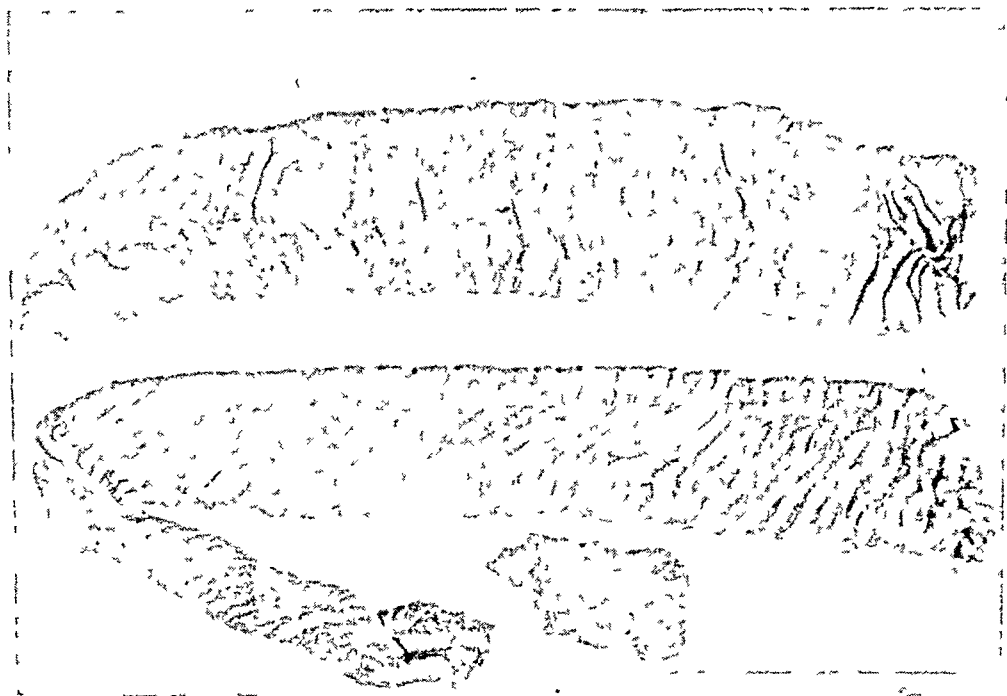


FIG. 2. Gross appearance of the thickened small bowel. At the bottom of the figure note the mass of enlarged mesenteric nodes.

phatase 8.6 Bodansky units; serum amylase was 65 Somogyi units. Stool examinations were negative for ova, parasites and occult blood; 57 per cent of the dried weight was fat, of which 28 per cent was fatty acid (present as stearic acid) and 72 per cent was neutral fat. A sugar tolerance test was as follows: Fasting 76 mg. per cent, after one-half hour 101 mg. per cent, after one hour 109 mg. per cent, two hours 108 mg. per cent, three hours 83 mg. per cent, four hours 76 mg. per cent, and at five hours 93 mg. per cent.

*Roentgenographic Examination.* Roentgenographic examination of the stomach was negative. Serial films of the small bowel showed marked segmentation, edema of the valvulae conniventes, and marked laking and stasis of barium in the small bowel. Roentgenographic studies following a barium enema revealed nothing abnormal. A chest roentgenogram showed pleural thickening in the right costophrenic sulcus.

*Course in Hospital.* Because the patient ate better when he was permitted to select his own diet, any attempt to regulate his food had to be abandoned. His diet was supplemented by vitamins and liver extract. He was also given frequent blood transfusions, plasma and glucose intravenously. At first the patient gained some weight, the stools became more formed and less profuse, and the borborygmi and tenesmus were calmed. But whatever veins were available soon became completely thrombosed so that intravenous therapy had to be discontinued. The patient ran a

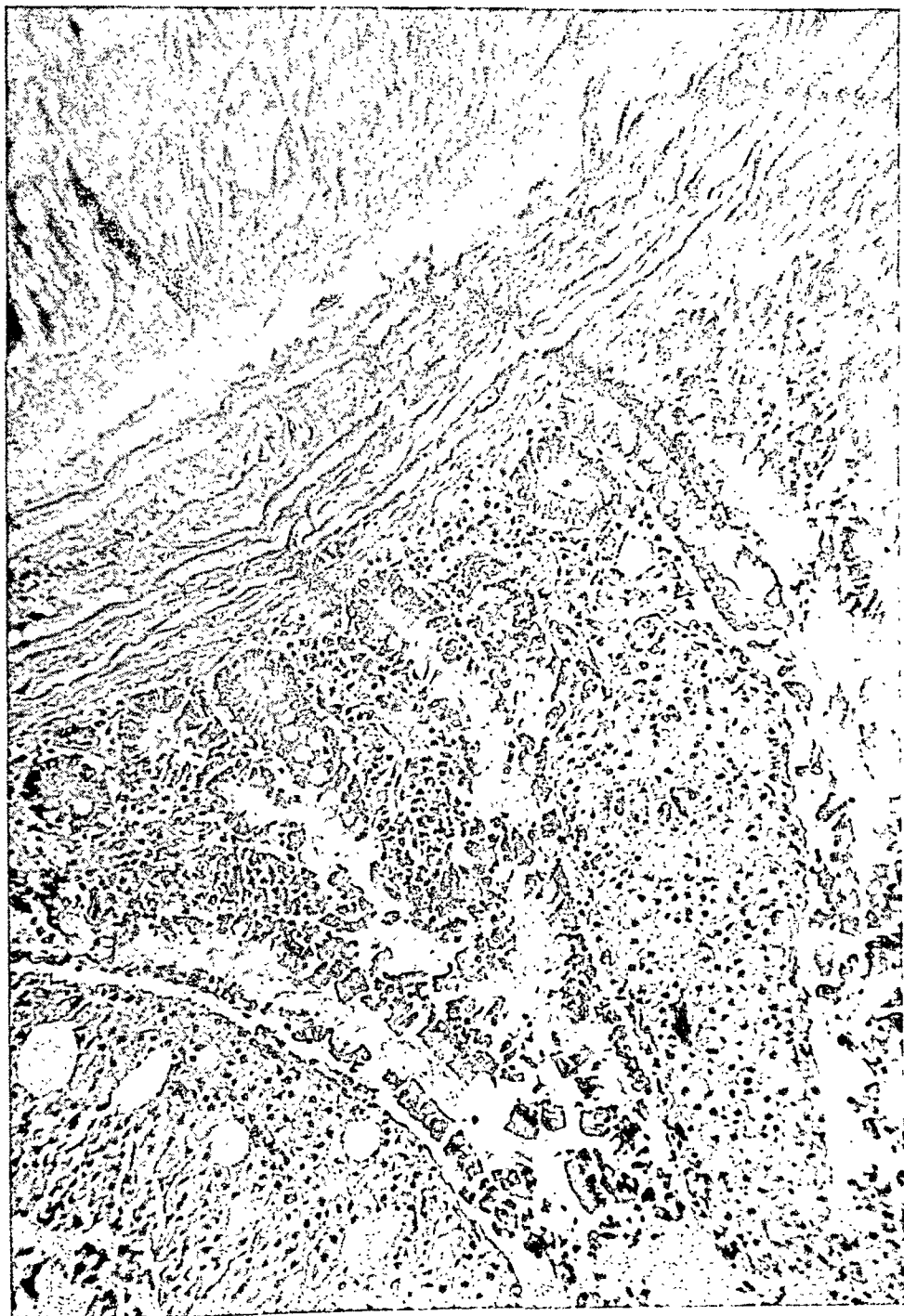


FIG. 3. Microscopic appearance of the small bowel. Note the enormously enlarged villi. Some vacuoles can be seen in the upper left corner.



low grade fever for which penicillin was given without relief. An area of redness 1 cm. in diameter appeared along the lateral margin in the midportion of the right leg. This area was covered by scales and resembled a psoriatic lesion. A similar lesion appeared on the right upper arm. Biopsy of the latter was interpreted as "slight hyperkeratosis and chronic dermatitis." The lesion on the leg disappeared spontaneously. The patient continued to run a fever of 102° F. to 103° F. The number of bowel movements was rarely more than seven daily; they were a battleship gray

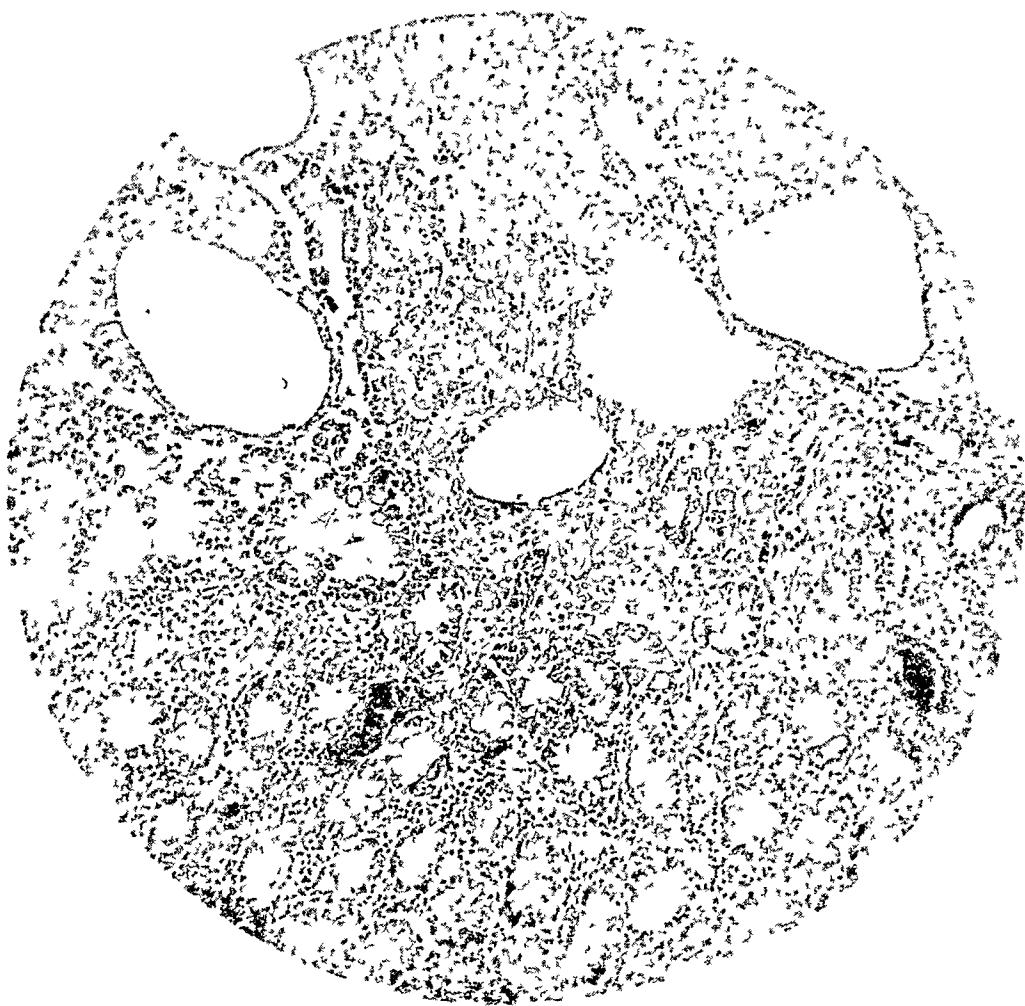


FIG. 4. Microscopic picture of the small bowel showing the vacuoles in the villi. Such vacuoles were also present in the submucosa.

in color and not foamy. About a week prior to his death he began complaining of a chest pain and a severe cough. He finally died in January 1946, 17 months after the onset of his illness.

*Postmortem Examination.* The postmortem examination was done eight hours after death. Chest: Numerous dense fibrous adhesions obliterated both pleural cavities and very little fluid was present. Both surfaces of the pleura were covered by a grayish white feathery exudate. Numerous areas of consolidation were noted in both lower lobes. The upper lobes appeared normal. The tracheal and bronchial

nodes were slightly enlarged. The heart weighed 375 grams; only about 20 c.c. of fluid were present in the pericardium. A few dense fibrous adhesions attached the pericardium to the anterior portion of the right ventricle. The pericardial surface was dull and was covered with a brown fibrinous exudate. The chordae tendineae were shortened and thickened. Abdomen: There were about 300 c.c. of cloudy thin fluid in the peritoneal cavity. The peritoneal surfaces were dull. There was marked mesenteric lymphadenopathy. Some of the nodular masses were 6 by 3 by 2.5 cm. The nodes were discrete and had a rubbery consistency. The liver weighed 1460

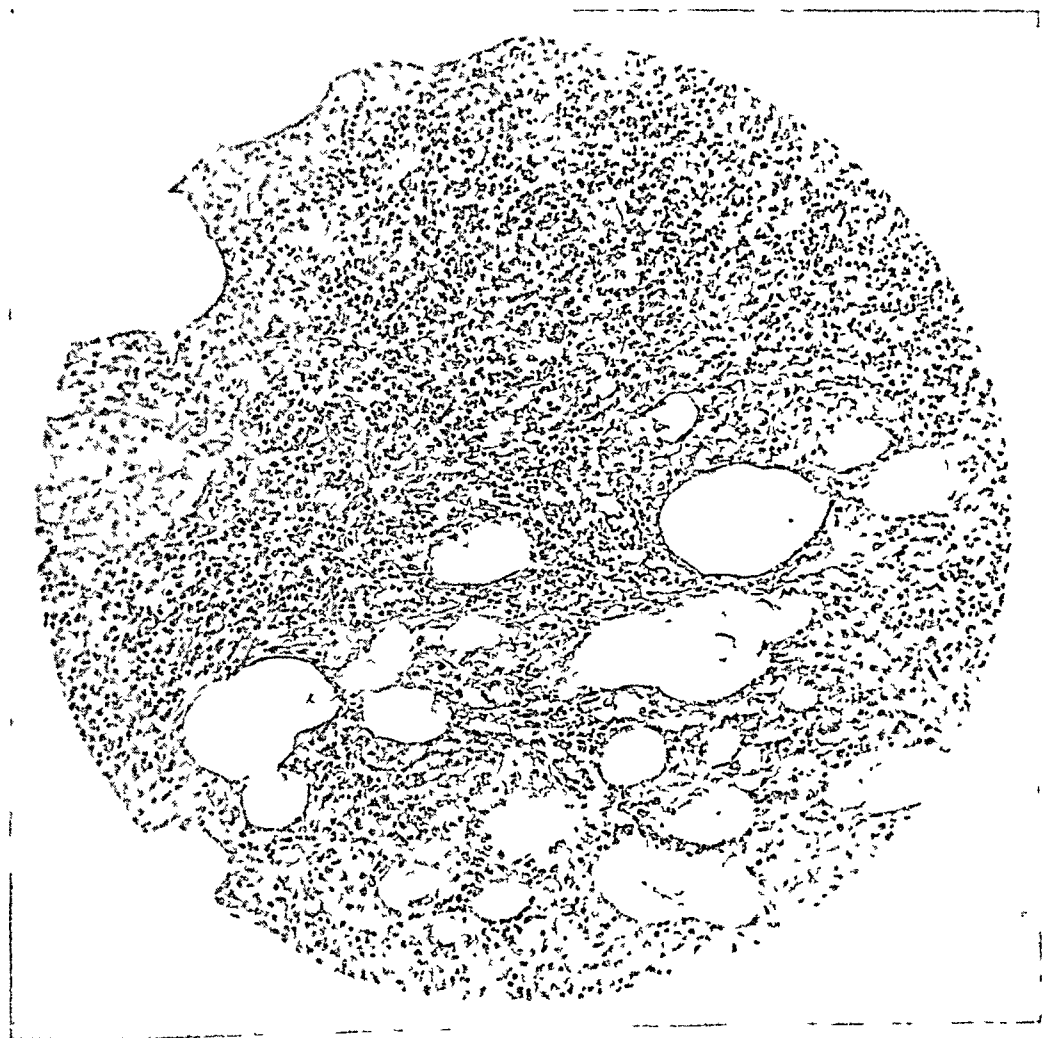


FIG. 5. Microscopic picture of a mesenteric node. The normal architecture has disappeared, the follicles are poorly preserved. Note the marked vacuolation.

grams. The external surface was covered by a shaggy fibrinous exudate very similar to that seen on the pleura and pericardium (figure 1). This exudate measured about 2 mm. in thickness. The normal lobular markings were somewhat obscured. No scarring or tumor was found. The gall-bladder appeared normal, the ducts were patent, and no stones were present. The spleen weighed 210 grams, and was covered with an exudate similar to that seen on the liver; it cut with increased resistance. The stomach was not grossly abnormal. The wall of the small intestine was markedly

thickened and edematous, most marked in the jejunum but also present in the ileum and duodenum. The entire small bowel was about twice the normal diameter (figure 2). The mucosa in particular was thickened and studded with granular grayish white flakes of various sizes which projected above the mucosal surface. The valvulae conniventes were very prominent and a lipoid substance exuded after the mucosa was cut. Gross examination of the colon, kidneys, pancreas, adrenals and brain showed no abnormalities.

The significant microscopic findings were limited to the small intestine, pleura, lungs, liver, lymph nodes and spleen. Small intestine (figures 3 and 4): All layers were thickened; some of the villi were three to four times wider and longer than normal. Large irregular vacuoles of various sizes were scattered throughout the villi, and in the submucosa large mononuclear foam cells were present. Fat stains identified these as cells containing lipids. Brunner's glands appeared normal. Mesenteric nodes (figure 5): The normal architecture was replaced by large irregular vacuolated areas which appeared to be lined by endothelium, and presented a swiss-cheese pattern. Only small islands of normal lymphoid cells remained. Numerous large mononuclear macrophages were noted showing a foamy cytoplasm. An occasional giant cell was noted. The lymphoid sinuses were greatly dilated. Lipoid globules were noted in the endothelial-lined cystic spaces. Liver: The capsule was irregularly thickened and lace-like villi projected from the endothelial surface. The fibrillar projections were lined by endothelium and contained lipoid and foam cells. The liver showed congestion about the central veins and moderate cell infiltration in the portal areas. The liver cells were granular, and fat vacuoles and foam cells were scattered throughout. Spleen: The splenic capsule showed the same appearance as that of the liver. The pulp showed congestion and condensation of the pulp reticulum. The follicles were poorly preserved. Lungs: The lungs showed patchy areas of consolidation in which the alveoli were distended with an exudate of round cells, plasma cells, large mononuclear cells and an occasional polymorphonuclear leukocyte. The exudate over the pleura and pericardium was identical with that described for the liver capsule. The other organs showed no pertinent changes. The pathological diagnoses were: (1) Intestinal lipodystrophy (Whipple's disease); (2) bronchopneumonia.

## DISCUSSION

The pathologic physiology of this disease is not known. For clinical and pathologic reasons this disease does not fit into any of the metabolic disorders such as Niemann-Pick, Hand-Schüller or Gaucher's diseases. The microscopic appearance suggests mesenteric obstruction to the lymph flow. The shaggy structures on the serous surfaces which on microscopic examination look like extensions of lymph channels, and the pleural and pericardial adhesions suggest an attempt on the part of the lymphatics to gain a new access to the veins. That the attempt is partially successful is evidenced by the relatively long duration of the disease and by the absence of chyle in either the thorax or abdomen; that the attempt is not quite successful is evidenced by the steatorrhea and markedly dilated lymphatics suggesting increased pressure within them, and of course by the patient's demise.

Where the lymphatic obstruction occurs must vary in each case. That occlusion of the thoracic duct is not necessarily the cause is evident by the findings of a patent thoracic duct where the latter was looked for, and in the absence of signs of lymphatic obstruction in diseases where the thoracic duct was actually occluded. The obstruction may be present at any point between the mesenteric nodes and

the opening of the thoracic duct into the subclavian vein. That this disease is so rare is probably due to the relative ease with which the lymph channels produce new anastomoses with the veins. Thus, Blalock and his associates,<sup>24</sup> in attempting to block the return of the lymph into the veins by 257 operations on 52 dogs and 22 cats, were successful in producing complete obstruction in only two animals. If the thoracic duct is occluded, new openings are made by the lymphatics into the inferior vena cava so that drainage of the former into the latter is satisfactorily accomplished.

A certain degree of similarity between regional enteritis and Whipple's disease suggests itself. In this respect, experiments of Reichert and Mathes<sup>25</sup> are of interest. These workers produced localized obstruction in the mesenteric channels, thus producing in the ileum a gross and microscopic picture not unlike that seen in regional enteritis. They believe that ileitis is produced by localized mesenteric lymph obstruction. It is conceivable that if obstruction in regional ileitis were distal to the mesenteric nodes and so extensive that lymphatic drainage from most of the small bowel were impaired, the microscopic appearance would be no different from that seen in Whipple's disease. The projection on the serous surfaces, the distended channels in the lymph nodes, and the presence of a large amount of lipid material are merely expressions of increased lymphatic obstruction. There is no impairment of fat absorption in regional ileitis because there is enough normal bowel left to accomplish this task satisfactorily.

### CONCLUSIONS

1. A case of Whipple's disease is reported. In general, it substantiates the clinical pattern of the disease as previously reported.

2. Diagnostic proof can be obtained only by laparotomy, if an exploratory operation is done when a disease other than Whipple's is suspected, or on post-mortem examination.

3. It is suggested that the pathologic physiology in Whipple's disease differs only in degree from that of other diseases in which there is lymphatic obstruction of the small intestine.

4. The rarity of Whipple's disease is due to the unusual ease with which lymphatic channels are able to establish new communications with the veins.

Appreciation is hereby expressed to Col. Ralph Thompson, of the Pathology Department of Percy Jones General Hospital, and to Dr. Plinn F. Morse, of the Harper Hospital, Detroit, for their interpretation of the microscopic sections.

### BIBLIOGRAPHY

1. SHERIDAN, P. E., and BAILEY, C.: Diabetic nocturnal diarrhea, *Jr. Am. Med. Assoc.*, 1946, cxxx, 632.
2. HANES, F. M.: Diagnostic criteria and resistance to therapy in the sprue syndrome, *Am. Jr. Med. Sci.*, 1942, cciv, 436.
3. HANES, F. M., and MCBRYDE, A.: Identity of sprue, non-tropical sprue, and coeliac disease, *Arch. Int. Med.*, 1936, lviii, 1.
4. THAYSEN, T. E. H.: *Non-tropical sprue*, 1932, Oxford University Press, London.
- 5a. BARGEN, J. A., BOLLMAN, J. L., and KEPLER, E. J.: The diarrhea of diabetes and steatorrhea of pancreatic insufficiency, *Proc. Staff Meet. Mayo Clin.*, 1936, ii, 737.
- 5b. BARGEN, J. A., BOLLMAN, J. L., and KEPLER, E. J.: The diarrhea of pancreatic insufficiency. *Am. Jr. Digest. Dis. and Nutr.*, 1938, iv, 728 (also note discussion by BOECK).

6. FAIRLEY, H. N., and MACKIE, F. P.: The clinical and biochemical syndrome in lymphadenoma and allied diseases involving the mesenteric glands, *Brit. Med. Jr.*, 1937, 1, 3972.
7. KLEIN, A., and PORTER, W. B.: Intestinal malabsorption associated with tuberculosis of mesenteric lymph nodes, *Arch. Int. Med.*, 1944, lxxiv, 120.
8. KILLIAN, S. T., and INGELFINGER, F. J.: Nutritional problems presented by a patient with extensive jejuno-ileitis, *Arch. Int. Med.*, 1944, lxxiii, 460.
9. MILLER, D. K., and BARKER, H. W.: Clinical course and treatment of sprue, *Arch. Int. Med.*, 1937, lx, 385.
10. WHIPPLE, G. H.: A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues, *Bull. Johns Hopkins Hosp.*, 1907, xviii, 382.
11. BLUMGART, H. L.: Three fatal adult cases of malabsorption of fat, *Arch. Int. Med.*, 1923, xxxii, 113.
12. FAIRLEY, H. N., and MACKIE, F. P.: The clinical and biochemical syndrome in lymphadenoma and allied diseases involving the mesenteric lymph glands, *Brit. Med. Jr.*, 1937, i, 375.
13. HILL, J. M.: Mesenteric chyloadenectasis. Report of a case, *Am. Jr. Path.*, 1936, xiii, 267.
14. JARCHO, S.: Steatorrhea with unusual intestinal lesions, *Bull. Johns Hopkins Hosp.*, 1936, lix, 275.
15. REINHART, H. L., and WILSON, S. J.: Malabsorption of fat (intestinal lipodystrophy of Whipple), *Am. Jr. Path.*, 1939, xv, 483.
16. RYLE, J. A.: Fatty stools from obstruction of lacteals, with note on coeliac affection, *Guy's Hosp. Rep.*, 1924, lxxiv, 1.
17. SAILER, S., and MCGANN, R. J.: Lipophagic granulomatosis of the enteric tract, *Am. Jr. Digest. Dis.*, 1942, ix, 55.
18. VAUX, D. M.: Chyloadenectasis with steatorrhea, *Jr. Path. and Bact.*, 1943, lv, 93.
19. GLYNN, L. E., and ROSENHEIM, M. L.: Mesenteric chyloadenectasis with steatorrhea and features of Addison's disease, *Jr. Path. and Bact.*, 1938, xlvii, 285.
20. FITZGERALD, P. J., and KINNEY, T. D.: Intestinal lipodystrophy (Whipple's disease), *Am. Jr. Path.*, 1945, xxi, 1069.
21. PEARSE, H. E.: Whipple's disease, *Surgery*, 1942, xi, 906.
22. AMSTERDAM, H. J., and GRAYZEL, D. M.: Intestinal lipodystrophy (lipophagia granulomatosis), *Am. Jr. Med. Sci.*, 1945, ccx, 605.
23. APPERLY, F. L., and COPLEY, E. L.: Whipple's disease (lipophagia granulomatosis), *Gastroenterology*, 1943, i, 461.
24. BLALOCK, A., ROBINSON, C. S., CUNNINGHAM, R. S., and GRAY, M. E.: Experimental studies on lymphatic blockage, *Arch. Surg.*, 1937, xxxiv, 1049.
25. REICHERT, L. R., and MATHES, M. E.: Experimental lymphedema of the intestinal tract and its relation to regional cicatrizing enteritis, *Ann. Surg.*, 1936, civ, 601.

---

## CIRCULATORY COLLAPSE FOLLOWING INTRAVENOUS ADMINISTRATION OF NICOTINIC ACID (NIACIN) \*

By BRUCE R. POWERS, M.D., F.A.C.P., *Knoxville, Tennessee*

NICOTINIC acid has come into widespread use not only because of its importance in the vitamin B complex but also because of its side action, vasodilatation. It is generally considered to be of low toxicity either given by mouth or by vein

\* Received for publication April 21, 1947.

and few untoward reactions have been reported. Some patients complain of the flush, itching, and sense of heat following either oral or intravenous administration and when doses sufficiently large to produce these signs of vasodilatation are given the patient should be told beforehand that the above phenomena will appear. These signs are desired and do not constitute toxic effects. Experimentally the difference between the therapeutic and toxic dose is very large.<sup>1</sup> An increase in skin temperature has been produced by reason of the increased blood flow. There are no regular changes produced in the blood pressure, pulse rate, respiration, oxygen consumption or electrocardiogram. I have administered the drug to patients with essential hypertension and followed them through the period of vasodilatation with frequent blood pressure and pulse rate determinations. No significant fall in blood pressure or change in pulse rate was found. A few patients have complained of dizziness following intravenous administration on resumption of the upright position. However, as this was the presenting symptom in most of these patients dizziness was not considered to be due to the drug.

Niacin has been advocated for its vasodilating properties in numerous conditions. Ménière's syndrome and migraine have probably received more attention than other conditions. I have used the drug in numerous patients with these syndromes and the reported patient is the only one manifesting a reaction. Perner<sup>2</sup> reports two patients in whom anaphylaxis occurred following intravenous administration of niacin. Both of these patients had prior medication with niacin or niacinamide and had unrevealed signs of previous mild allergy to the drug. Both of his patients recovered following prompt administration of epinephrine.

#### CASE REPORT

This patient was white, a male 65 years old who complained of marked dizziness and vertigo for seven to ten days. He had no tinnitus or headaches. He gave a history of chronic cough which was productive of a large quantity of gray sputum in the morning. He had dyspnea on slight exertion. Three months previously he had been hospitalized for accentuation of cough and dyspnea. Roentgenographic studies gave evidence of a pneumonitis and it was also felt that he had early congestive heart failure. He improved following hospitalization for one month. Later roentgenographic studies showed disappearance of abnormal shadows in the lung fields. However, he continued to have cough and exertional dyspnea. He gave no personal history of allergic manifestations; but one sibling had severe chronic bronchial asthma. Another sibling has severe congestive heart failure. The patient had taken niacin previously in multiple vitamin preparations.

He appeared to be chronically ill and poorly nourished. His complexion was markedly sallow. He had no dyspnea at rest. A prominent arcus senilis was present. There were a few basal râles posteriorly. The apex beat of the heart was in the fifth interspace at the midclavicular line. The rhythm was regular, rate 90 per minute, and no murmurs were present. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. The peripheral arteries were tortuous and hard. Examination of the oral cavity, abdomen, and rectum gave findings consistent with the patient's age. I considered that he had a disturbance involving his labyrinth, and that therapy with niacin was indicated.

He was placed in the recumbent position on the table and niacin 10 mg. per c.c. (Lilly) was started intravenously. This was given slowly as is my usual procedure. No flush was noted. When he had received 25 to 30 mg. of the preparation he complained of feeling faint and that he was blacking out. His voice was less strong. He had become definitely cyanotic. His pulse became rapid, weak and then imper-

ceptible. His respirations were slow and shallow and his skin was cold and clammy. He appeared to be in a definitely precarious position. The niacin was discontinued at the onset of these signs and 0.5 c.c. of epinephrine was given intramuscularly. His pulse again became palpable but continued weak and rapid. He was given an additional 0.3 c.c. of epinephrine in 10 minutes. His color, pulse, and respirations slowly improved and at the end of an hour he appeared to be out of danger. He told me after this occurrence that a few days earlier while in a barber shop for a shave he almost blacked out when the barber chair was changed to the recumbent position. He was unable to stay in this position. However, when the reported incident occurred in my office he had been recumbent for several minutes before circulatory failure occurred, so I am inclined to feel that recumbency itself was not causative. At no time did he have pain or any choking feeling in his chest. He was able to walk from the office about two hours after the reaction occurred. He had no recurrence of circulatory failure.

### SUMMARY

A patient manifesting severe shock during administration of niacin is reported. Circulatory stability was reestablished at the end of one hour; epinephrine was promptly injected at the onset of the reaction.

Niacin is a drug of low toxicity and reactivity. The possibility of sensitivity should be considered. If the drug is given intravenously, slow administration is advisable with the patient under continuous observation.

### BIBLIOGRAPHY

1. GOODMAN, LOUIS, and GILMAN, ALFRED: The pharmacological basis of therapeutics, 1st Edition, 1941, Macmillan Co., New York, N. Y., pages 1254-1258.
2. PELNER, LOUIS: Anaphylaxis to the injection of nicotinic acid (niacin); successful treatment with epinephrine, *Ann. Int. Med.*, 1947, xxvi, 290-293.

## EDITORIAL

### LOWER NEPHRON NEPHROSIS

INTENSIVE study, beginning in 1941,<sup>1</sup> of the clinical aspects, pathology, and abnormal physiology of the crush syndrome led soon to the realization that the renal disturbances were not peculiar to this entity but were, in fact, to be observed in many diseases. Bywaters and Dible<sup>2</sup> drew attention to the fact that the syndrome, which they had previously thought to be a new one, had as a matter of fact been recognized by German clinicians and pathologists in World War I. A review of these cases had been published in 1923 by Minami.<sup>3</sup> Moon<sup>4</sup> observed that many of the predominant features of the syndrome were quite well known to clinicians and pathologists of an earlier era under a variety of names of which acute parenchymatous nephritis or acute tubular nephritis were perhaps the most widely used. He stated that the widespread usage and popularity of the Volhard and Fahr<sup>5</sup> classification of renal diseases which entirely omits mention of acute parenchymatous nephritis, may have been partially responsible for the lapse of interest in, and knowledge of, the syndrome. Be that as it may, there has been a growing realization that this entity, first described in relation to injuries of military origin, is perhaps one of the commoner renal diseases being encountered in a diversity of diseases having little, if any, military connotations.

Even during the past several years, problems of terminology have tended to hinder the full-fledged emergence of this syndrome as a clinical entity. These problems are, perhaps, of more than semantic interest, since variations in nomenclature have often connoted an incomplete understanding of basic mechanisms involved in the production of the syndrome. Thus many essential features of this entity are to be observed in cases of so-called pre-renal azotemia,<sup>6</sup> a concept which often has to be abandoned when the postmortem examination shows organic renal damage. Hemoglobinuric nephrosis, a term used recently by Mallory,<sup>7</sup> tends, perhaps, to emphasize unduly an aspect of the disease which need not always be present in classical examples. Lucké<sup>8</sup> has recently proposed the term, lower nephron nephrosis, for the

<sup>1</sup> BYWATERS, E. G. L., and BEALL, D.: Crush injuries with impairment of renal function, *Brit. Med. Jr.*, 1941, i, 427-432.

<sup>2</sup> BYWATERS, E. G. L., and DIBLE, J. H.: Renal lesion in traumatic anuria, *Jr. Path. and Bact.*, 1942, liv, 111-120.

<sup>3</sup> MINAMI, S.: Über Nierenveränderungen nach Verschüttung, *Virchow's Arch. f. path. Anat.*, 1923, ccxlv, 247-267.

<sup>4</sup> MOON, V. H.: Hemoglobinuric or tubular nephrosis (acute parenchymatous nephritis). *N. Carolina Med. Jr.*, 1948, ix, 238-242.

<sup>5</sup> VOLHARD, F., and FAHR, T.: *Die Brightsche Nierenkrankheit*, 1914, Julius Springer, Berlin, 292 p.

<sup>6</sup> FISHBERG, A. M.: *Hypertension and nephritis*, 1939, 4th Ed., Lea and Febiger, Philadelphia, Pa., pp. 55 et seq.

<sup>7</sup> MALLORY, T. B.: Hemoglobinuric nephrosis in traumatic shock, *Am. Jr. Clin. Path.*, 1947, xvii, 427-443.

<sup>8</sup> LUCKÉ, B.: Lower nephron nephrosis, *Mil. Surg.*, 1946, xcix, 371-396.



syndrome. This name appears to be already achieving widespread clinical popularity so that its use conjures up a specific syndrome. It possesses the advantage of localizing the renal lesion while at the same time avoiding commitment in the vexed question of the predominance of renal anoxia or various nephrotoxins as the principal etiological factors. Many factors in the etiology still remain obscure as will be observed below.

In addition to the crush syndrome, lower nephron nephrosis has been observed in the following conditions: non-traumatic muscular ischemia,<sup>9</sup> burns,<sup>10</sup> hemolytic transfusion reaction,<sup>11</sup> heat stroke,<sup>12</sup> blackwater fever,<sup>13</sup> toxemias of pregnancy,<sup>14</sup> sulfonamide intoxication,<sup>15</sup> the so-called hepatorenal syndrome,<sup>16</sup> and poisonings with certain vegetable and chemical agents.<sup>17</sup> Two common denominators are present in virtually all of these disease processes, namely, tissue or blood destruction, and shock of varying degree. It is probable that both of these factors operate synergistically to produce the clinical and pathological features of lower nephron nephrosis. The manner in which they do so has been elucidated in recent years by many significant physiological and biochemical investigations. However, before launching into a discussion of these observations, it would be well to present briefly the clinical and pathological features of the syndrome.

In view of the varied etiology it is somewhat difficult to present a single comprehensive clinical picture. Suffice it to say, that after some mishap, involving either extensive tissue injury or destruction, or blood destruction, followed by a transient interval of shock, the patient is observed to become oliguric or even anuric. Such urine as may be passed is highly acid, has a low, fixed specific gravity and may often be bloody, port-wine colored or smoky in appearance. The passage of heme pigmented urine is not universally present. The nature of the pigment, whether it be hemoglobin or myohemoglobin, can usually be ascertained by spectroscopic study. Proteinuria of a moderate degree is usually present and the sediment usually contains granular or pigmented casts. Chemical studies of the blood will reveal a progressive rise in non-protein nitrogen, at times an increase in potassium

<sup>9</sup> BYWATERS, E. D. L., and DIBLE, J. H.: Acute paralytic myohaemoglobinuria in man, *Jr. Path. and Bact.*, 1943, *lv*, 7-15.

<sup>10</sup> LUND, C. C., GREEN, R. W., RAYLOR, F. H. L., and LEVENSON, S. M.: Burns: collective review, *Surg., Gynec. and Obst.*, 1946, *lxxxii*, 443-478.

<sup>11</sup> DE NAVASQUEZ, S.: Excretion of hemoglobin, with special reference to "transfusion" kidney, *Jr. Path. and Bact.*, 1940, *li*, 413-425.

<sup>12</sup> MALAMUD, N., HAYMAKER, W., and CUSTER, R. P.: Heat stroke, *Mil. Surg.*, 1946, *xcix*, 397-449.

<sup>13</sup> MAEGRAITH, B. G., and FINDLAY, G. M.: Oliguria in blackwater fever, *Lancet*, 1944, *ii*, 403-404.

<sup>14</sup> PAXSON, N. F., GOLUB, L. J., and HUNTER, R. M.: Crush syndrome in obstetrics and gynecology, *Jr. Am. Med. Assoc.*, 1946, *cxxxi*, 500-504.

<sup>15</sup> FRENCH, A. J.: Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy, *Am. Jr. Path.*, 1946, *xxii*, 697-701.

<sup>16</sup> SCHUTZ, C. B., HELWIG, F. C., and KUHN, H. P.: A contribution to the so-called liver death, *Jr. Am. Med. Assoc.*, 1932, *xcix*, 633.

<sup>17</sup> GRUBER, G. B., in HENKE, F., and LUBARSCH, O.: *Handb. d. spez. path. Anat. u. Histol.* V-6, pt-2, 1934, J. Springer, Berlin.

and phosphate, and a decrease in alkali reserve. The blood pressure, after recovery from the initial shock phase, tends to rise to moderate hypertensive levels. Edema is usually insignificant. Most aspects of the uremic syndrome will be observed and in fatal cases death in typical uremic coma is usual. The mortality rate is high. Lucké<sup>8</sup> states it to be approximately 90 per cent, with death occurring anywhere from 2 to 30 days after onset. It must be remembered that most cases hitherto have been observed and managed under what would hardly be called optimal conditions. Those cases which recover, either spontaneously or as the result of correct therapeutic management, begin to show a diuresis which is often characterized by the excessive loss of sodium and chloride in the urine. Ultimately there is a complete return to normal renal function.

The pathological picture encountered in fatal cases is characteristic. The kidneys are swollen and pale. Cross-section reveals widening and pallor of the cortex which stands out in sharp contrast to the medullary zone which is dark and has accentuated striations. The characteristic histopathology is observed in the distal portion of the nephron, involving the epithelium of the thick limb of Henle and the distal convoluted tubules. These areas of the nephron exhibit focal patches of cellular degeneration and necrosis. Some lumina contain casts of a heme compound. There may be moderate edema and cellular reaction in the stroma about the more severely damaged tubules, and adjacent thin-walled veins often exhibit parietal thrombi.

The syndrome of lower nephron nephrosis is encountered commonly in individuals who have managed to survive for some time following a period of sub-lethal shock. Obviously, patients in profound shock will usually die of circulatory failure prior to the development of specific renal pathology, while those only mildly shocked will usually not develop any significant renal damage. It may be rewarding to review briefly some of the fundamental disturbances in renal circulation which accompany shock of varied etiology. The occurrence of shock is accompanied by contraction of the vascular bed by peripheral constriction so that the diminished volume of available blood will be adequate to supply such vital organs as the brain whose function must be maintained to avoid immediate death.<sup>18</sup> In hemorrhagic shock, for example, with severe blood loss, the kidneys are included in the constricted periphery. In time of deficit, they appear to stand intermediate between the skin and muscle which can survive long periods of ischemia, and the central nervous system which can survive almost none.<sup>19</sup> Undue prolongation of the period of deficient blood supply apparently results in organic renal damage of the type described above. Van Slyke<sup>18</sup> conveniently divides the phases of renal failure in shock into an initial, functional, rever-

<sup>18</sup> VAN SLYKE, D. D.: The effects of shock on the kidney, *Ann. Int. Med.*, 1948, xxviii, 701-722.

<sup>19</sup> GREEN, H. D., COSBY, R. S., and LEWIS, R. N.: Modification of blood flow in skin and muscle of dogs in hemorrhagic shock, *Fed. Proc.*, 1942, i, 32, Part II.

sible phase due primarily to circulatory deficit and a second phase, persisting after recovery from shock, attributable to organic injury, which may or may not be reversible. The duration of shock and renal circulatory impairment is of vital significance. Renal failure, associated with persistent oliguria or anuria after recovery from shock, does not necessarily imply a progressive renal lesion. As a matter of fact, the renal damage may be looked upon as having occurred during the period of shock only. From that time onward the fate of the patient, from a renal standpoint, will depend literally on a race between the progressing azotemia and gradual repair of the renal injury.

There is apparently still some controversy over the mechanism of renal circulatory impairment during shock. According to Van Slyke et al.<sup>18</sup> this is due, primarily, to renal vaso-constriction, their opinion being based upon the observation that renal blood flow, measured by the clearance of para-amino hippurate, is diminished. On the other hand, Trueta et al.<sup>20</sup> have proposed a somewhat different mechanism for the renal ischemia. In a series of experiments on rabbits, they observed that the application of a tourniquet to one of the hind legs for a period of hours resulted in an alteration of the circulation in the homolateral kidney. This was characterized by an apparent increase in renal circulation but only through part of the kidney. There was a bypassing of the renal cortical vascular channels via the medulla. The bypassing seems to occur through what are called the juxtamedullary glomeruli thereby effectively producing cortical ischemia. Ultimate judgment concerning these concepts must, for the time being, be left subjudice. It is fascinating to speculate upon the possibility of the Trueta mechanism as the etiological factor in a related renal syndrome, bilateral symmetrical cortical necrosis, observed in rare instances following shock, in post-partum or post-operative patients.

Since the syndrome of lower nephron nephrosis is observed following a variety of traumata, it is inevitable that the renal pathology be considered as resulting from the action of a nephrotoxin. Critical consideration of the syndrome forces one to tend to adhere to the concept of the primacy of renal anoxia induced by renal circulatory deficit. Nevertheless there is considerable evidence pointing toward the importance of a nephrotoxic agent. A major difficulty in the acceptance of the idea of a nephrotoxin lies in the diversity of these agents. There is still some controversy over the toxicity of free hemoglobin or myohemoglobin. However, the consensus seems to be that solutions of pure hemo- or myohemoglobin<sup>11</sup> are not nephrotoxic. Nephrotoxic effects occurring after injection of these compounds have been attributed to abnormal breakdown products or derivatives such as hematin (sodium ferrihemate).<sup>21</sup> The latter substance also produces intense renal vaso-constriction so that it is somewhat difficult to know whether tubular damage is due to primary cellular injury or is secondary to vaso-constriction.

<sup>20</sup> TRUETA, J., BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., and PRITCHARD, M. M. L.: Studies of the renal circulation, 1947, Blackwell Scientific Publications, Oxford, 187 p.

<sup>21</sup> ANDERSON, W. A. D., MORRISON, D. B., and WILLIAMS, E. F.: Pathologic changes following injections of ferrihemate (hematin) in dogs, Arch. Path., 1942, xxxiii, 589-602.

Other products of tissue breakdown have also been observed at times to have a nephrotoxic effect. It has been suggested<sup>22</sup> that toxic products liberated from injured tissue are detoxified by the liver if the rate of release into the blood stream is sufficiently slow, but that this mechanism does not operate efficiently with excessive flooding of the circulation.

With the establishment of organic renal damage, oliguria and anuria become cardinal features of the syndrome. There seems to be little doubt that the anuria of the early shock phase is directly related to the fall in arterial pressure below a critical level necessary to maintain glomerular filtration. In the second or renal damage phase several mechanisms may be operative. For many years the rôle of tubular obstruction by heme pigment casts has been the subject of controversy. The weight of evidence seems to be against this as an important factor. Some of the reasons cited include: (1) the number of tubules observed to be obstructed appears to be inadequate to explain failure of excretion of urine; (2) the syndrome can occur in the absence of heme pigment casts; (3) there is little if any dilatation of glomerular spaces and upper segments of the tubule which should be observed with obstruction. Oliver<sup>23</sup> has recently revived interest in the rôle of obstruction as a result of his studies on individually dissected nephrons. It seems likely, however, that a more important mechanism producing oliguria is the unselective reabsorption of glomerular filtrate by damaged tubular epithelium. Richards<sup>24</sup> by direct observation of the living frog's kidney, noted that after poisoning by mercuric chloride even though glomerular filtration remained quite active, no urine could be seen to emerge from the ureters. In other words, there was literally a "leaking" back of filtrate into the blood of the peri-tubular capillaries. The tubular walls, devitalized by poison, approached dead membranes in their behavior. The entire glomerular filtrate, both water and solutes, passed indiscriminately back presumably drawn by the osmotic attraction of the plasma proteins for the filtrate water. The application of this concept to the human kidney of lower nephron nephrosis must still be considered as a tentative rather than a demonstrated explanation for the anuria. It has been suggested also that increased intrarenal pressure, offering abnormal resistance to glomerular filtration, may likewise be a factor in the anuria.<sup>25</sup>

As a result of the recent delineations of the clinical, pathological and physiological features of this syndrome, therapeutic management should offer more hope of success. It is important to maintain, constantly, the concept that this is a self-limited disease which, if survival is achieved, will be followed ultimately by complete recovery of renal function. It is beyond the scope of this brief summation to discuss details of therapeutic manage-

<sup>22</sup> EGGLETON, M.: Crush kidney syndrome in the cat, *Lancet*, 1944, ii, 208-210.

<sup>23</sup> OLIVER, J.: New directions in renal morphology: a method, its results, and its future, *Harvey Lectures*, 1945, xl, 102-155.

<sup>24</sup> RICHARDS, A. N.: Direct observations of change in function of renal tubule caused by certain poisons, *Trans. Assoc. Am. Phys.*, 1929, xlv, 64-67.

<sup>25</sup> PETERS, J. T.: Oliguria and anuria due to increased intrarenal pressure, *Ann. Int. Med.*, 1945, xxiii, 221.

ment. Nevertheless, certain principles can be stressed: (1) prevention is feasible in regard to certain of the precipitating causes, e.g., hemolytic transfusion reaction, sulfonamide intoxication, etc.; (2) termination of shock as quickly as possible by the use of whole blood, plasma, human albumin solution or other infusion fluids will reduce the period of renal anoxia and thereby diminish organic renal damage; (3) *avoidance of overhydration during the period of oliguria or anuria*; (4) increased use of several methods of treatment still looked upon as in their clinical infancy, e.g., the "artificial kidney,"<sup>26</sup> and peritoneal irrigation<sup>27</sup>; (5) careful observation of the serum chloride level during the diuresis phase of recovery so as to circumvent the occurrence of hypochloremia.

The very diversity of the precipitating causes of lower nephron nephrosis virtually insure its frequent clinical occurrence in almost every variety of medical practice. Understanding of many of the basic mechanisms involved has already been achieved and should lead to reduction in mortality.

M. S. S.

<sup>26</sup> KOLFF, W. J., and BERK, H. R. J.: The artificial kidney: a dialyzer with great area, *Acta med. Scandin.*, 1944, cxvii, 121.

<sup>27</sup> FINE, J., FRANK, H. A., and SELIGMANN, A. M.: The treatment of acute renal failure by peritoneal irrigation, *Ann. Surg.*, 1946, cxxiv, 857.

## REVIEWS

*Psychiatry in a Troubled World: Yesterday's War and Today's Challenge.* By WILLIAM C. MENNINGER, M.D. 636 pages; 16 × 24.5 cm. The Macmillan Co., New York. 1948. Price, \$6.00.

This is by far the most important book on psychiatry in World War II so far published. The author was, for the major part of the war, Chief Consultant in Neuropsychiatry to the Surgeon General. He describes, with much documentation, the size and characteristics of the task, the errors made, the obstacles encountered and the results achieved. He demonstrates how the lessons learned in World War I were almost completely ignored and forgotten by the Army before World War II. The last part of the book deals with the possible application of lessons learned in the recent War to post-war civilian problems. Because of the extensive uses of source material and bibliography the book will serve as an extremely useful reference book in any study of the applications of psychiatry to military medicine, medical education, criminology, industry and medicine in general.

H. W. N.

*Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior.* 2nd Ed. By WENDELL MUNCIE, M.D. 620 pages; 17 × 25 cm. The C. V. Mosby Co., St. Louis, Mo. 1948. Price, \$9.00.

This book is an official and formal exposition of Meyerian psychiatry. It is a textbook "aimed primarily for the use of students." It is recommended as a good description of the teaching of Adolf Meyer. Its biggest weakness, however, is that it ignores the outstanding contributions made to modern dynamic psychiatry by various workers in the field of psychoanalysis.

H. W. N.

*Mental Mischief and Emotional Conflicts. Psychiatry and Psychology in Plain English.* By WILLIAM S. SADLER, M.D., F.A.P.A., Chicago. 396 pages; 16 × 24 cm. The C. V. Mosby Co., St. Louis, Mo. 1947. Price, \$6.00.

Even if Dr. Sadler's book were written, as claimed, in "plain English," the reviewer still would recommend it neither to the layman nor professional reader. The concepts offered are not in keeping with present-day psychiatric thinking. His personal opinions regarding etiology, mental mechanisms and therapy are neither scientific, sound nor practical in the reviewer's opinion.

H. W. N.

*Symposium on Medicolegal Problems, under the Co-Sponsorship of the Institute of Medicine of Chicago and the Chicago Bar.* Edited by SAMUEL S. LEVINSON for the Committees of the Institute of Medicine and the Chicago Bar Association. 255 pages; 13 × 20 cm. J. B. Lippincott Co., Philadelphia. 1948. Price, \$5.00.

This small book represents a praiseworthy effort on the part of the Chicago Bar Association and the Chicago Institute of Medicine to bring some order into the chaos of medicolegal work. The method of presentation is that of a symposium. First doctors and then lawyers discuss each problem from their respective viewpoints. The ensuing general discussion and questions are faithfully transcribed. All of the speakers are men of undisputed ability in their respective fields. Among the important problems discussed are expert testimony, artificial insemination, medicolegal pathology, sterilization and scientific tests in evidence.

The method of presentation is subject to the unevenness and personal bias that typify any group discussion but it serves to bring into form various points of conflict between medical and legal minds. Probably such differences in outlook can never be entirely settled, as the legal emphasis on absolute truth and on precedent is so fundamentally different from the medical stress on the working hypothesis and the reserving of judgment. It is only through such joint discussions as this book records that mutual understanding if not agreement may be achieved.

There is much in this volume both of stimulus and of helpful information for any physician doing medicolegal work.

H. J. M.

*A Textbook of Clinical Neurology.* 2nd Ed., Revised. By J. M. NIELSEN, M.D., F.A.C.P. 699 pages; 18.5 × 26 cm. Paul B. Hoeber, Inc., New York. 1946. Price, \$7.50.

This book of neurology has been written especially for the student and the general practitioner. It can be used as an introduction to neurology as well as a brief reference book. Neurological diseases are discussed in this text in a neuroanatomical order, such as diseases of the peripheral nerves, spinal cord, cranial nerves, brain stem, cerebellum, thalamus, basal ganglia and cerebrum. There are individual sections related to epilepsy, migraine, trauma to the brain and the spinal cord, degenerative diseases, idiocy, congenital diseases, avitaminosis as well as a chapter on the psychoneuroses. There is a chapter devoted to the fundamentals of electroencephalography. Each chapter has an adequate, up-to-date bibliography. The chapter on inflammations and intoxications is very well written. The book is brief, well written and contains many plates and diagrams which are better than average.

W. L. F.

*Urologic Roentgenology.* 2nd Ed., Revised. By MILEY B. WESSON, M. D., Ex-President, American Urological Association. 259 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1946. Price, \$5.50.

The author's aim to provide a *vade mecum*, rather than a treatise, has been faithfully accomplished. As an introduction to this specialized field this volume will be very welcome.

The material is presented in a factual manner and yet warnings are interjected to impress the reader that radiological evidence alone must be supplemented and corroborated by clinical study before a final diagnosis is accepted. Perhaps these warnings could have been repeated more often by the author.

The radiological findings and differential diagnoses are well presented. All the illustrations are excellent. A well chosen bibliography is furnished at the end of each chapter.

H. D. V.

#### BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Correlative Neuroanatomy.* 4th Ed. By JOSEPH J. McDONALD, M.S., M.Sc.D., M.D., JOSEPH G. CHUSID, A.B., M.D., and JACK LANGE, M.S., M.D. 156 pages; 25 × 17.5 cm. (loose-leaf, paper-bound). 1948. University Medical Publishers, Palo Alto, California. Price, \$3.00.

- A Course in Practical Therapeutics.* By MARTIN EMIL REHFUSS, M.D., F.A.C.P., Professor of Clinical Medicine and Sutherland M. Prevost Lecturer in Therapeutics, The Jefferson Medical College, Philadelphia, etc.; F. KENNETH ALBRECHT, M.D., Formerly Clinical Director U. S. Marine Hospital, Baltimore, etc., and ALISON HOWE PRICE, A.B., M.D., Asst. Professor of Medicine, The Jefferson Medical College, Philadelphia, etc. 824 pages; 29 × 22.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$15.00.
- Diseases of the Ear, Nose and Throat.* By WILLIAM WALLACE MORRISON, M.D., Professor of Otolaryngology and Attending Otolaryngologist, New York Polyclinic Medical School and Hospital, etc. 772 pages; 24.5 × 16 cm. 1948. D. Appleton-Century Company, Inc., New York. Price, \$8.50.
- "Elective Alimentary Rest" and the Elimination of So-Called "Paralytic Ileus" after Abdominal Operations.* By V. J. KINSELLA, M.B., Ch.M. (Syd.), F.R.C.S., F.R.A.C.S. 35 pages; 21.5 × 14 cm. (paper-bound). 1948. Angus & Robertson, Ltd., Sydney, Australia. Price, 3/.
- General Endocrinology.* By C. DONNELL TURNER, Ph.D., Associate Professor of Zoology at Northwestern University. 604 pages; 24.5 × 16 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$6.75.
- Give Them a Chance to Talk: Handbook on Speech Correction for Cerebral Palsy.* By BERNEICE R. RUTHERFORD. 116 pages; 23 × 15 cm. (paper-bound). 1948. Burgess Publishing Company, Minneapolis. Price, \$2.75.
- Hemolysis and Related Phenomena.* By ERIC PONDER, The Nassau Hospital, Mineola, New York. 398 pages; 24 × 15.5 cm. 1948. Grune & Stratton, Inc., New York. Price, \$10.00.
- How Laymen Cut Medical Costs.* 35 pages; 22.5 × 15 cm. 1948. Public Health Institute, Chicago. Distributed without cost.
- Investigations on Agonal Acidosis.* By IB FABRICIUS HANSEN. 135 pages; 26.5 × 18.5 cm. (paper-bound). 1948. Povl Branner, Copenhagen, Denmark. Price, \$3.00.
- The Mechanism of Abdominal Pain.* By V. J. KINSELLA, M.B., Ch. M. (Syd.), F.R.C.S. (Eng.), F.R.A.C.S., Hon. Surgeon, St. Vincent's Hospital, Sydney, etc. 230 pages; 25.5 × 15 cm. 1948. Angus & Robertson, Ltd., Sydney, Australia. Price, 32/6.
- Practice of Allergy.* 2nd Ed. By WARREN T. VAUGHAN, M.D., Richmond, Virginia. Revised by J. HARVEY BLACK, M.D., Dallas, Texas. 1132 pages; 26.5 × 17.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$15.00.
- Racial Variations in Immunity to Syphilis: A Study of the Disease in the Chinese, White, and Negro Races.* By CHESTER NORTH FRAZIER and LI HUNG-CHIUNG. 122 pages; 23.5 × 15.5 cm. 1948. The University of Chicago Press, Chicago. Price, \$2.50.
- Roentgen Studies of the Lungs and Heart: A Series of Lectures Delivered at the Center for Continuation Study, University of Minnesota.* By NILS WESTERMARK, M.D., Director, Department of Radiology, St. Göran's Hospital, Stockholm, Sweden. Edited by LEO G. RIGLER, M.D., Professor of Radiology, University of Minnesota. 216 pages; 27 × 17.5 cm. 1948. University of Minnesota Press, Minneapolis. Price, \$7.00.



- The Skull, Sinuses and Mastoids: A Handbook of Roentgen Diagnosis.* By BARTON R. YOUNG, M.D., Professor of Radiology, Temple University Medical School. 328 pages; 21 × 14.5 cm. 1948. The Year Book Publishers, Inc., Chicago. Price, \$6.50.
- Treatise on Surgical Infections.* By FRANK LAMONT MELENEY, M.D., Associate Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University, etc. 713 pages; 24.5 × 16 cm. 1948. Oxford University Press, New York. Price, \$12.00.
- Twentieth Century Speech and Voice Correction.* Edited by EMIL FROESCHELS, M.D., President, International Society for Logopedics and Phoniatics, etc. 321 pages; 21.5 × 14 cm. 1948. Philosophical Library, New York. Price, \$6.00.
- Venous Thrombosis and Pulmonary Embolism.* By HAROLD NEUHOF, M.D., Clinical Professor of Surgery in Columbia University, etc. 159 pages; 26 × 17.5 cm. 1948. Grune & Stratton, Inc., New York. Price, \$4.50.

## COLLEGE NEWS NOTES

### RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949–June 30, 1950. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for proper pursuit of his work. The stipend will be from \$2,200 to \$3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

---

### A.C.P. POSTGRADUATE COURSES

*Autumn, 1948*

The Preliminary Bulletin of Postgraduate Courses, published early in July, presented the calendar and description of the eight courses arranged by the American College of Physicians between August and December, 1948. Course No. 1, "Cardiology," at the National Institute of Cardiology, Mexico, and Course No. 2, "Internal Medicine with Emphasis on Pathological Physiology," at the University of Cincinnati, have been concluded, the latter course with maximum registration. Course No. 3, "Internal Medicine," at the University of Pittsburgh, is in progress, with a large registration (limited to 50).

Course No. 6, "Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease," at the Massachusetts General Hospital, Boston, November 15–24, has been filled to capacity since the middle of August.

At the time of the preparation of this announcement, August 15, accommodations are still available in the following courses:

No. 4, "Internal Medicine"  
University of Michigan Medical School  
Ann Arbor, Mich.  
Dr. C. C. Sturgis, Director  
One Week—October 18–29

No. 5, "Endocrinology"  
University of Illinois College of Medicine (classes meeting at the LaSalle Hotel, Chicago)  
Chicago, Ill.  
Dr. Willard O. Thompson, Director  
One Week—November 1–6.

No. 7, "Cardiovascular Disease"  
Emory University School of Medicine  
Atlanta, Ga.  
Dr. R. Bruce Logue, Director  
One Week—December 6–11

## No. 8, "Gastro-enterology"

Graduate Hospital of the University of Pennsylvania

Philadelphia, Pa.

Dr. Henry L. Bockus, Director

One Week—December 6–11

All inquiries should be addressed to the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

---

## REGULAR AUTUMN MEETING, BOARD OF REGENTS

The regular autumn meeting of the various committees and of the Board of Regents will be held at Philadelphia, November 5, 6 and 7.

The Committee on Nominations will meet Friday, November 5; the Committee on Credentials, November 5 and 6; all other committees, on November 6; the Board, on November 7. Proposals of candidates for membership in The College must be filed sixty days in advance of action. Next succeeding meetings of the Committee on Credentials will be held in late February and on March 26, 1949.

---

The American College of Physicians has added to its roster of Life Members the names of Jacob L. Tuechter, M.D., F.A.C.P., Cincinnati, Ohio, and Gilbert E. Brereton, M.D., F.A.C.P., Dallas, Tex. The endowment funds of the College have been augmented by their subscriptions to Life Membership.

---

## CONTRIBUTIONS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the kindness of Franklin H. Top, M.D., F.A.C.P., Detroit, Mich., who recently gave to the College Library of Publications by Members a copy of his new 2nd Edition of the "Handbook of Communicable Diseases," published by The C. V. Mosby Company, St. Louis, 1947.

Acknowledgment is made also of receipt of the Handbook of the Royal College of Physicians and Surgeons of Canada, and of copies of the Annual Lectures of that College for 1947, sent through the kindness of J. E. Plunkett, M.D., F.A.C.P., Ottawa, Honorary Secretary of the Royal College. A.C.P. Fellows listed in the Handbook as officers and Council members include: Dr. D. Sclater Lewis, Montreal, Vice President; W. F. Connell, Kingston, H. K. Detweiler, Toronto, Ray F. Farquharson, Toronto, Richard Lessard, Quebec, and A. G. McGhie, Hamilton, members of the Council representing the Division of Medicine.

---

## AMERICAN BOARD OF INTERNAL MEDICINE

Revision, July 1, 1948

## MEMORANDUM TO APPLICANTS FOR ADMISSION TO EXAMINATION

In the November, 1947, issue of the ANNALS OF INTERNAL MEDICINE, Volume 27, No. V, page 845, appeared the revised memorandum to applicants for admission to the examinations of the American Board of Internal Medicine. Further revisions have now taken place as of July 1, 1948, and are hereunder published.

## I. *General Qualifications*

### C. Change to read as follows:

All candidates must be active members in good standing in their County and State medical societies in the state of legal residence. Under unusual and exceptional circumstances the Board reserves the privilege of modifying this requirement.

(This ruling shall not apply to commissioned officers of the United States regular Army or Navy or United States Public Health Service who are otherwise members of the American Medical Association.)

## II. *Professional Qualifications*

- I. The Board will grant one year of graduate training credit, or one year in satisfaction of the requirements of practice, regardless of assignment, for active duty as a commissioned officer in the United States Army, Navy, or United States Public Health Service for one year or more, beginning on or subsequent to December 7, 1941 and terminating on or before January 1, 1947. Commissioned officers serving less than one year prior to January 1, 1947 may apply that interval as graduate training.

### *Application*

#### Paragraph 3

The application must be accompanied by one recent, signed photograph of the candidate mounted on the application, and the registration and examination fee of forty dollars, which fee will cover both the written and oral examinations. An additional fee of ten dollars will be required when the certificate is issued.

### *Method of Examination*

#### Paragraph 1

. . . The written examination is held simultaneously in different sections of the United States and Canada on the third Monday of October of each year.

### *Re-examination*

#### Paragraph 3

. . . A fee of twenty dollars is required for each additional oral examination.

#### Paragraph 4

Candidates who have taken one written examination or one oral examination while on active duty overseas as a commissioned officer in the United States Army, Navy, or Public Health Service will be authorized to take a fourth written examination or a fourth oral examination if necessary. This regulation will not apply to candidates in the Armed Forces who took their written or oral examinations in the United States.

---

## THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

"In order to facilitate the arrangements for training in child psychiatry (which constitutes a major aspect of modern psychiatry), the American Board of Psychiatry and Neurology will accept one year of training in psychiatric clinics for children which may or may not be a part of a hospital approved for residency training, provided such a clinic gives adequate supervision and instruction for full-time training during the entire third year of the required three-year formal training period. For the purpose of evaluating such clinics, the following conditions and criteria are deemed essential by the American Board of Psychiatry and Neurology:

1. That the clinic have a full-time medical director, psychologist, and social worker qualified by training and experience in child psychiatry and allied fields to supervise the training of residents;
2. That the major portion of such training be devoted to therapy adequately supervised by this qualified staff;
3. That the service and teaching activities of the clinic be integrated with those of the community and its social agencies;
4. That clinic work be supplemented by seminars, case conferences, journal clubs or other opportunities for the discussion of the basic principles involved in outpatient work with children and parents, teacher, public health and welfare agency personnel;
5. That such a training clinic be well established in the community with a qualified staff that has operated together long enough as a team to insure stable and sound functioning;
6. That the senior members of the clinic team show evidence of previous experience in the teaching of psychiatry in general, child psychiatry in particular, and their allied fields.

"These criteria set forth by the Board pertain more particularly to community-sponsored clinics offering full-time training in child psychiatry during the third year of formal residency training. If these clinics are affiliated with hospitals already maintaining approved programs, separate approval is not required unless warranted on the basis of their meeting all requirements for straight fellowship training in child psychiatry.

"The following clinics are acceptable to the American Board of Psychiatry and Neurology as qualifying under these provisions:

#### *Clinic*

#### *Director*

Children's Psychiatric Division, Langley Porter Clinic, San Francisco, California.	Dr. Stanislaus Szurek
Bureau of Mental Hygiene, 1179 Main Street, Hartford, Connecticut.	Dr. Jas. M. Cunningham
Louisville Mental Hygiene Clinic and Child Study School, 610 South Floyd Street, Louisville, Kentucky.	Dr. Spafford Ackerly
The Guidance Center, 1737 Prytania Street, New Orleans, Louisiana.	Dr. Milton E. Kirkpatrick
The Psychiatric Clinic of the Mental Hygiene Society of Maryland, Baltimore, Maryland.	Dr. H. Whitman Newell
Children's Center, 244 Townsend Street, Roxbury, Massachusetts.	Dr. Marian Putnam and Mrs. Beata Rank, co-directors
Judge Baker Guidance Center, 38 Beacon Street, Boston, Massachusetts.	Dr. George E. Gardner
Amherst H. Wilder Clinic, 379 Rice Street, St. Paul, Minnesota.	Dr. Hyman S. Lippman
Central Clinic, Cincinnati General Hospital, Cincinnati, Ohio.	Dr. Maurice Levine
Child Guidance Center, 1711 Fitzwater Street, Philadelphia 46, Pennsylvania.	Dr. Frederick H. Allen
Pittsburgh Child Guidance Clinic, 3004 Victoria Street, Pittsburgh 13, Pennsylvania.	Dr. Harry M. Little
Children's Service Center of Wyoming Valley, 335 South Franklin Street, Wilkes-Barre, Pennsylvania.	Dr. J. Franklin Robinson

### AMERICAN COLLEGE OF CHEST PHYSICIANS OFFERS POSTGRADUATE COURSE

The American College of Chest Physicians has announced its first annual post-graduate course presenting the newer aspects of diseases of the chest at the Hotel New Yorker, New York City, November 8 to 12, 1948. Applications for the course should be addressed to their Executive Offices, 500 North Dearborn Street, Chicago 10, Ill.

---

### CONTINUATION COURSE IN DISEASES OF THE DIGESTIVE TRACT

The Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, 2020 E. 93rd St., Cleveland 6, Ohio, has scheduled a continuation course in DISEASES OF THE DIGESTIVE TRACT to be given at the Cleveland Clinic Building on Thursday, Friday, and Saturday, October 7, 8, and 9, 1948. Among guest teachers, other than members of the Clinic staff, are Dr. Lester R. Dragstedt, F.A.C.P., Chicago, Illinois, and Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pennsylvania. Dr. Edwin P. Jordan, F.A.C.P., is the Director of Education of the Institute.

---

### AMERICAN ACADEMY OF ALLERGY ORIENTATION COURSE IN ALLERGY

The American Academy of Allergy has announced an Orientation Course in Allergy, to be given during the week of October 25 to 29, inclusive, 1948, at Northwestern University Medical School. Inquiries should be addressed to Samuel M. Feinberg, M.D., Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill.

---

### GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

An intensive graduate instructional course in allergy will be presented by The American College of Allergists under the auspices of the University of Oregon Medical School, Portland, Oregon, November 8 to 12, 1948, inclusive. Hotel headquarters will be at the Heathman Hotel. The Course includes all phases of the subject and will be represented by specialists in the fields of the basic sciences, as well as specialists in allergy, detailing treatment and management of the allergic patient. There will be panel discussion and demonstrations of technics. Printed comprehensive abstracts of the lectures are furnished the registrants. The Course is available to members and non-members of the College. Applications should be placed with Dr. Fred W. Wittich, Secretary, 423 La Salle Medical Building, The American College of Allergists, Minneapolis 2, Minnesota. Programs will be mailed upon request. The charge for the Course is \$75.00 payable at the registration desk.

---

The American Public Health Association will hold its 77th Annual Meeting in New York City during the week of October 23, 1949. Its 76th Annual Meeting will be held in Boston, November 8 to 12, 1948.

---

The 1949 Assembly of the Interstate Postgraduate Medical Association of North America will be held in Philadelphia, Pa., the week of October 31, 1949.

---

### REGIONAL MEETING ON DISASTER PREPAREDNESS HELD AT PHILADELPHIA

Representatives from surrounding States and the District of Columbia attended a special meeting on Disaster Preparedness at The Philadelphia County Medical Society on June 8, the purpose of the Conference being to formulate a uniform plan

of organization to provide emergency medical care in the event of an atomic disaster.

Dr. Perrin H. Long, member of the A.M.A. Emergency Medical Council, and at present assigned to the Office of Atomic Warfare in Washington, reported on plans being formulated to cope with any atomic disaster. Technical sections are being planned for transportation, disasters, policing, fire control, engineering, chemical and biological warfare, radiologic defense and medicine. The medical section will be divided into the Public Health Service, the Administration Service and the Medical Care Service. Under the Public Health Service will fall conveniences which are normal in any large city within the Department of Health, such as protection of food, milk and water. The Administration Service will be concerned with hospitalization and evacuation problems. The Medical Care Service will include physicians and persons in allied fields to take care of the ill and injured. It is planned to create eight technical mobile groups, which can be moved speedily to disaster scenes. Physicians will be evaluated, so that their professional abilities may be used to the best advantage. It is anticipated that a definite program will be evolved in Washington.

---

#### NEED FOR INTERNISTS IN VETERAN ADMINISTRATION HOSPITALS

Branch Office No. 5 of the VA, Atlanta 3, Ga. appeals to the internists of the United States to help them staff the 17 hospitals under their jurisdiction. There are abundant opportunities for physicians who are qualified in internal medicine and the subspecialties to head services and sections in these hospitals which are located throughout the southeast from Johnson City, Tennessee to Tuscaloosa, Alabama, and from Memphis, Tennessee to Coral Gables, Florida.

In addition to openings for specialists, there are also abundant opportunities for young men who have finished their residency training, and who now need two or more years of preceptorship training, under certified internists, with teaching ability, where they may make their final preparation in an academic atmosphere for completion of the American Board requirements.

The organization plan of all of our hospitals follows the outline prepared by the Council on Medical Education and Hospitals published by the American Medical Association (Jr. Am. Med. Assoc., 1939, cxiii, 794). Emphasis is placed on bedside instruction, teaching rounds, seminars, clinical-pathological conferences, demonstrations and lectures. All of our hospitals are affiliated with nearby medical schools for educational purposes and twenty qualified Branch Consultants; covering every specialty in Medicine and Surgery, pay periodic visits to the hospitals for teaching and supervision of the professional service in their respective fields.

All of our hospitals possess large well-equipped laboratories and libraries. All new modern textbooks and an average of 100 current journals are available to the staff doctors. Opportunities for research and study are splendid. Every possible consideration is given to the encouragement and stimulation of clinical investigation and professional advancement. Attendance at conventions and postgraduate courses is approved on official leave. Excellent bibliographical and medical illustration service is available to all of our doctors upon request.

Salaries, while they are not high, the upper limit being \$11,000.00 per year, are adequate for those physicians who are interested primarily in professional advancement, an opportunity to contribute to the medical literature, or who have an overwhelming desire to practice top-flight medicine in an atmosphere of professional freedom.

There are other advantages to participation in the new Department of Medicine and Surgery of the VA including 30 days of annual leave and retirement privileges, but the greatest inducement of all is the ability to practice first class medicine without being hampered by the inevitable consideration of the cost of medication, special examinations and laboratory procedures, consultation service or lengthy hospitalization,

such as inevitably affects the character of professional services rendered by the civilian physician in private practice. Satisfaction in the splendid service rendered to worthy veterans and their heartfelt gratitude expressed to the physician undoubtedly plays a great part in the professional morale so high in our hospitals. There has been a great improvement in every phase of hospital service since the renaissance spear-headed by Dr. Paul R. Hawley and promoted, expanded, and brought into full-flower through the efforts of our present Chief Medical Director, Dr. Paul B. Magnuson.

Present openings in our hospital are as follows:

1. Chief of Medical Service, Montgomery VA Hospital; 300-bed general medical and surgical hospital, located in the city of Montgomery, Alabama; population of 110,000 people. We also need seven other younger internists at this hospital. This is the only general VA Hospital in the State of Alabama, and the clinical material is excellent for teaching and research. The educational program in this hospital is carried on under the auspices of the University of Alabama Medical School.

2. Chief of Medical Service, Dublin, Georgia. This is the former Naval Hospital located about 45 miles from Macon, Georgia. This hospital has just been opened and for the time being is functioning as a 200-bed general hospital. The educational program in this hospital will be carried on under the auspices of Emory University Medical School.

3. Chief of Medical Service, Murfreesboro, Tennessee; 900-bed Neuropsychiatric Hospital with small general medical and surgical unit. The Chief of Service would serve as a consultant to the other services and could, if acceptable to the Dean's Committee, also serve as a part-time teacher at Vanderbilt University in Nashville, some 32 miles from Murfreesboro. The educational program at this hospital is being carried on under the auspices of Vanderbilt University Medical School.

4. Chief of Medical Service, Mountain Home, Tennessee. We have six openings for internists interested in training in the various subspecialties of Internal Medicine under the supervision of two certified specialists in the hospital located at Mountain Home near Johnson City, Tennessee. The educational program carried on in this hospital is under the auspices of Bowman-Gray Medical School, Winston-Salem, North Carolina.

5. We have four openings for medical residents at our VA Hospital, Coral Gables, Florida.

6. We also have vacancies for 17 additional internists throughout the Branch and the following specialists:

Orthopedic Surgeons	3	
Anesthesiologists	7	
X-ray Specialists	6	
Otolaryngologists	2	
Pathologists	5	
Physical Medicine	5	
Diseases of the Chest	8	
Psychiatrists	24	
Residents	12	(openings in NP, Radiology, Pathology, and Anesthesiology)

---

At the Annual Meeting of the American College of Radiology, held in Chicago in June, 1948, Dr. E. P. Pendergrass, F.A.C.P., Philadelphia, was elected president for the 1948-49 year, and Dr. J. Edwin Habbe, F.A.C.P., Milwaukee, was elected to the Board of Chancellors.



Robert H. Williams, M.D., F.A.C.P., formerly Associate Professor of Medicine in the Harvard Medical School, became Professor of Medicine and executive officer of the department in the University of Washington School of Medicine on July 1.

---

Dr. Tinsley R. Harrison, F.A.C.P., Dallas, Tex., has succeeded Arlie R. Barnes, M.D., F.A.C.P., Rochester, Minn., as president of the American Heart Association.

---

George C. Turnbull, F.A.C.P., Evanston, Ill., has been appointed Attending Physician to the Cook County Hospital, as of July 1.

---

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., was recently elected president of the newly organized Connecticut Diabetes Association. Membership in this society will include physicians, members of allied professional groups, diabetics and their relatives, and those otherwise interested in the control of the disease. One of the principal efforts of the society will be the development of an educational program.

---

Anthony C. Cipollaro, M.D., F.A.C.P., New York, N. Y., was elected Chairman of the Section on Dermatology and Syphilology of the American Medical Association during the recent Chicago meeting. He was also recently appointed Professor and attending dermatologist and syphilologist in the New York Polyclinic Medical School and Hospital.

---

Dr. Sidney W. Jennes, F.A.C.P., Waterbury, Conn., was elected the first president of the Connecticut State Allergy Society, which held its first meeting during the recent annual meeting of the Connecticut State Medical Society.

---

Dr. John W. Shuman, Sr., F.A.C.P., Santa Monica, Calif., has been made an Honorary Fellow of the American Geriatrics Society.

---

Kenneth M. Smith, M.D., F.A.C.P., accepted full-time appointment in August with the Veterans Administration as Chief of Medicine and Acting Chief of Tuberculosis for Michigan, Ohio and Kentucky. Dr. Smith will retain his appointment in the Ohio State University as Assistant Professor of Medicine. His office will be at 52 S. Starling St., Columbus 8, Ohio.

---

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., Editor of the Mississippi Valley Medical Journal, has set up an irrevocable trust known as the Swanberg Kiwanis Foundation, "to sponsor, undertake, or aid in one or more things of a charitable, scientific, literary, or education nature," the trust to be administered by nine trustees, at least one of whom must be a physician. Dr. Swanberg has twice served as president of the Kiwanis Club of Quincy.

---

Dr. James A. Brussel (associate), Assistant Director of the Willard State Hospital, has been awarded first and second prizes in the 1948 national contest of the American Physician's Literary Guild, which was held in conjunction with the A.M.A. convention in June.

## OBITUARIES

## DR. GUY WILLIAM WELLS

Guy William Wells, M.D., a Fellow of the American College of Physicians since 1931, died in Providence, R. I., on June 15, 1948, in his 57th year.

A native of Pennsylvania, Dr. Wells received his college and medical education at Brown University and Cornell University Medical College. After an internship at the Rhode Island Hospital and a residency in Medicine at the Peter Bent Brigham Hospital, he entered the practice of internal medicine in Providence and thereafter made his home in that city. He rose to a position of medical leadership in his community and, during the last two years of his life, served as Chief of the Medical Service in both the Pawtucket Memorial and the Rhode Island Hospitals. Dr. Wells devoted much time to the work of his local and state medical societies. From 1936 to 1941, he served as Secretary to the Rhode Island Medical Society and, during 1947, was President of the Providence Medical Association. Both before and after World War II, he was the member from Rhode Island to the House of Delegates of the American Medical Association.

At heart a deeply patriotic citizen, Dr. Wells early in his career joined the Medical Reserve Corps of the U. S. Army, rising to the rank of Major, and in July, 1941, was called to active duty. Following assignments as Chief of the Medical Service of the Station Hospital, Camp Devens, Mass., and on procurement duty for medical officers in Rhode Island, he became Commanding Officer of the 52nd Station Hospital. His unit was among the first to land in North Africa after the invasion, and its record throughout the African and the subsequent Italian campaigns was one of outstanding merit. A tribute to Dr. Wells' service and patriotism was made in the following messages sent by two of his superior officers on learning of his death:

From General Mark Clark:

... His unselfish devotion to duty during our campaigns in Italy endeared him to us all. Together with his countless friends I salute the passing of a loyal soldier and a real friend to man. . . .

From Brig. Gen. J. J. Martin, (M.C.), U.S.A.:

... American medicine and particularly the Army, which he loved so much, have lost a pillar of strength which can never be replaced. As a doctor, a military leader, and a gentleman he had no peer. The many thousands of his comrades who were carried through the trying days of the last war by his unfailing cheerfulness and his uncanny ability to lead the way to the best horizons will bear into eternity the mark of his presence. . . .

Guy Wells was a man of wide popularity with a genuine capacity for friendship. He was conspicuously a gentleman, endowed with tolerance and consideration for the feelings of others. He was by nature a clinician and in practice a very thoughtful and practical doctor. In his positions of leadership it was invariably his way to seek counsel from those under him and to make them feel they shared leadership with him. His death at the peak of his active career is keenly felt by all of his friends, associates and contemporaries.

MARSHALL N. FULTON, M.D., F.A.C.P.

## DR. CHARLES CAMILLE DE GRAVELLES

Dr. Charles Camille de Gravelles, F.A.C.P., of New Iberia, La., died on March 22, 1948, of coronary occlusion, at the age of 65. A graduate of the Tulane University of Louisiana School of Medicine in 1910, Dr. de Gravelles achieved prominence in the medical circles of his native state of Louisiana early in his career, and

was known to everyone as a capable, conscientious and highly ethical practitioner. He was president of the Louisiana State Medical Society in 1943, and was elected to Fellowship in the American College of Physicians in 1930. By his death the medical profession of Louisiana loses one of its most distinguished members.

EDGAR HULL, M.D., F.A.C.P.,  
Governor for Louisiana

### COLONEL GEORGE DAVIES CHUNN

George D. Chunn, a Fellow of the American College of Physicians since 1927, died at Tampa, Fla., March 12, 1948, at the age of 59. A graduate of the University of Arkansas and of the Johns Hopkins University School of Medicine, Dr. Chunn entered the Medical Corps of the U. S. Army in 1914. Among his assignments were posts of Chief of Medical Service of the Station Hospitals at Fort Leavenworth, Kans. and Fort Bragg, N. C. He also served as Commanding Officer of Station Hospital No. 2 at Fort Bragg. Dr. Chunn retired from the service in October, 1945.

Dr. Chunn was a diplomate of the American Board of Internal Medicine, a fellow of the American Medical Association, and a member of The Association of Military Surgeons of the United States.

### DR. HENRY SNURE

Dr. Henry Snure died at his home in Los Angeles, Calif., on May 17, 1948. He was born at Lakefield, Minn., November 4, 1887, and obtained his preliminary education at Concordia College, St. Paul. In 1910 he was graduated from the University of Louisville School of Medicine and he practiced in Ohio and Michigan until 1916 at which time he came to California.

During World War I, Dr. Snure served at the United States Naval Hospital, Mare Island, as pathologist. Since that time he had limited his practice to radiology and was for many years the roentgenologist for the California, and California Babies' and Children's Hospitals in Los Angeles. He was a Diplomate of the American Board of Radiology and a Fellow of the American College of Radiology. He became a Fellow of the American College of Physicians in 1929. He served as a Councilor for the Los Angeles County Medical Association for many years and was granted retired membership in this Association in December, 1945.

Dr. Snure was a kindly man and was always willing to help members of the profession with difficult problems. He will be greatly missed in Los Angeles.

LELAND HAWKINS, M.D., F.A.C.P.,  
Governor for Southern California

### DR. JOHN BARR McALISTER

John B. McAlister, Harrisburg, Pa., died on July 22, 1948. Born in Carroll County, Md., in 1864, Dr. McAlister attended Gettysburg College which he later served as Trustee, and the University of Pennsylvania School of Medicine, from which he received his medical degree in 1877. He served the Harrisburg Hospital for many years as Visiting Physician and as Medical Director. Following his retirement, he was appointed an Honorary Life Member of the staff of that hospital.

Dr. McAlister was a former president of the Harrisburg Academy of Medicine, Dauphin County Medical Society, and the Medical Society of the State of Pennsylvania. He was elected a Fellow of the American College of Physicians in 1926.

## DR. EDWIN JACOB SCHISLER

Dr. Edwin Jacob Schisler, F.A.C.P., St. Louis, Mo., died January 12, 1948. He was born at St. Louis in 1874. He received his medical degree from Beaumont Hospital Medical College, later the St. Louis University School of Medicine, in 1896. During his early career, he was Associate in Medicine at St. Louis University School of Medicine and filled various appointments on the staffs of Alexian Brothers Hospital, the Lutheran Hospital, St. Louis City Hospital, and in later years was Consulting Physician to the Alexian Brothers, St. Anthony's and St. John's Hospitals. For several years he was Physician to the Evangelical Deaconess Home and Hospital. He was a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1923.

## DR. ALEXANDER V. GRISWOLD, SR.

Dr. Alexander Viets Griswold, Sr., of Louisville, Ky., died suddenly in his 86th year, on June 22, 1948.

A graduate in 1886 of the University of Louisville School of Medicine, Dr. Griswold interned in the Bellevue Hospital and the Louisville City Hospital, and practiced general medicine in Louisville to the day of his death.

An Associate of the American College of Physicians by virtue of membership in the old American Congress on Internal Medicine, Dr. Griswold was one of the first physicians from Louisville to become a member of that organization, in 1917.

## DR. ROBERT HUGH McDONALD

Robert Hugh McDonald, M.D., F.A.C.P., died at his home in Cleveland, Ohio, Sunday, July 20, 1947, from an attack of coronary thrombosis. At the time of his death he was a staff member of the Department of Medicine of the Cleveland Clinic.

Dr. McDonald was born in Oxford County, Ontario, Canada, on October 19, 1895. He attended the University of Toronto Faculty of Medicine, where he was an honor student throughout his course and won the Gold Medal when he obtained the degree of M.B. in 1922. During the following three years, he was a house officer in the Toronto General Hospital. Dr. John Phillips brought him to Cleveland where he spent his remaining years as a member of the Cleveland Clinic staff.

Elected a Fellow of the American College of Physicians in 1939, Dr. McDonald was an active member of The Academy of Medicine of Cleveland, Cleveland Medical Library, American Medical Association, and College of Physicians and Surgeons of Ontario.

In his work in the diagnostic clinic, Dr. McDonald developed a broad knowledge of the entire field of internal medicine; his chief interest, however, lay in diseases of the kidney. An earnest and conscientious worker, he endeared himself to his patients and associates.

DR. RUSSELL L. HADEN, M.D., F.A.C.P.

## DR. FRANK JAMES ROHNER

Frank James Rohner, M.D., F.A.C.P., died at his home in Iowa City, Iowa, on July 1, 1947, after an illness of several years. He was born at Carroll, Iowa, July 11, 1882. He received his M.D. degree at the State University of Iowa School of Medicine in 1912. He subsequently served that School as Lecturer in Medicine, 1915-20, Assistant Professor of Medicine, 1920-26, and Associate Professor of Medicine, 1926-27. He then engaged in private practice in Iowa City.

Dr. Rohner was a member of Alpha Omega Alpha, Johnson County and Iowa State Medical Societies, Central Society for Clinical Research, and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians in 1931.

Dr. Rohner was extremely popular as a teacher, and was regarded by his colleagues and students as an unusually capable clinician. Until his health failed he was in demand as a consultant over a large part of his State. His unfortunate illness removed him from the practice of medicine when he had barely reached his prime. He will long be remembered by his many students and associates as a keen diagnostician and an inspiring teacher and friend.

B. F. WOLVERTON, M.D., F.A.C.P.,  
Governor for Iowa

### DR. STEPHEN SMITH

Stephen Smith, M.D., F.A.C.P., died suddenly of coronary thrombosis at his home in Pasadena, Calif., on June 3, 1947. His loss was felt deeply by his numerous patients and his colleagues.

Dr. Smith was born at Ellicottville, N. Y., in 1880. He attended the University of Michigan, where he majored in Organic Chemistry under Dr. Victor Vaughn and received his M.D. degree from the Medical School in 1905. In 1907, after service at the Lakeside Hospital in Cleveland, he went to Pasadena to become associated with Dr. James McBride, Director of Las Encinas Sanitarium (then known as the Southern California Sanitarium). When Dr. McBride retired in 1909 Dr. Smith assumed full control of the institution.

Although he was trained in internal medicine, he saw early in his career at Las Encinas that there was a deep and very close relationship between functional disorders of the psyche and many physical illnesses. He found too often that only by the solution of all the problems relating to the patient, emotional as well as physical, could a lasting cure be effected. In short, he practiced that phase of medicine now termed psychosomatic long before it was recognized as such.

Dr. Smith pursued this course with great success but in time felt that the developments in the study of psychiatry had become so great that they outstripped his fundamental knowledge of this new field of medicine. In his efforts to provide more complete and competent treatment to all aspects of internal medicine he realized that psychiatry held a prominent part in the program and he therefore allied himself with specialists in that field in order that the patient might be treated as a whole being, mind as well as body.

His interest in the human ailments led him further along the path devoted to the efforts of medicine to prolong the life of the individual. Soon he was giving much of his time to the treatment of the aged and to the diseases peculiar to that group. Here again, he began these activities long before the practice of geriatrics was viewed as a clinical specialty.

Dr. Smith was elected a Fellow of the American College of Physicians in 1924, and was certified by the American Board of Internal Medicine in 1937.

Dr. Stephen Smith is remembered not only by his many patients for his firm and thoughtful treatment, guidance and advice in their difficulties, but also by his colleagues to whom he afforded an institution for the treatment of various chronic and acute diseases, unique in its type.

CHARLES W. THOMPSON, M.D., F.A.C.P.

## DR. GEORGE WADE WILSON

George Wade Wilson, M.D., F.A.C.P., formerly of St. Louis, Mo., died on June 6, 1947, in California, where he had resided and practiced for a number of years.

Dr. Wilson was born in St. Louis in 1891. He attended St. Louis University from which he received the degrees of Bachelor of Arts in 1910, Master of Arts in 1913, and Doctor of Medicine in 1914. Following internship in the Providence Hospital, Washington, D. C., Dr. Wilson became affiliated with the staffs of the Jewish, Barnes, and Missouri Pacific Hospitals in St. Louis. His academic and research appointments were Assistant in Medicine and Pathology, St. Louis University School of Medicine, 1916-17; Fellow and Assistant in Pathology and Bacteriology, Rockefeller Institute for Medical Research, 1917-19; Professor and Head of Department of Pathology, Bacteriology, and Preventive Medicine, Loyola University School of Medicine, 1919-20; Associate in Medicine, Washington University School of Medicine, 1920-24. Following his removal to the Coast, Dr. Wilson became affiliated with the University of Southern California School of Medicine, in which he held the title of Associate Professor of Clinical Medicine.

Dr. Wilson was elected a Fellow of the American College of Physicians in 1923.

## DR. WILLIAM PEPPER

Dr. William Pepper, Dean Emeritus of the University of Pennsylvania School of Medicine, died December 3, 1947, at the age of 73.

Dr. Pepper retired two years ago after serving as Dean of the Medical School for 33 years. His death was attributed to coronary thrombosis. He was the third William Pepper to serve the University of Pennsylvania in a distinguished position. His grandfather held the chair of theory and practice of medicine from 1860 to 1864, and his father was provost and professor of medicine from 1881 to 1894. Dr. Pepper was a cousin of the former U. S. Senator George Wharton Pepper and a direct descendant of Benjamin Franklin. He held the degrees of A.B., M.D., and D.Sc., from the University of Pennsylvania and an honorary doctorate of laws from Temple University. He contributed many articles to leading medical journals and was a member of many scientific societies and a former President of the Association of American Medical Colleges. He was also a trustee of the University of Pennsylvania. He is survived by two sons, William Pepper, Jr., an officer of the Philadelphia Free Library, D. Sergeant Pepper, M.D., F.A.C.P., Assistant Medical Director of the Provident Mutual Life Insurance Company, a daughter, Mrs. Mary Pepper Parker, and a brother, O. H. Perry Pepper, M.D., M.A.C.P., Professor of Medicine in the University of Pennsylvania.

All of the many who knew Dean Pepper will recall the sympathetic and good humored interest with which those who consulted him were received, and the absolute integrity which even the most casual acquaintance perceived in him. His long and distinguished career covered a vital period of transition in medical education. In his passing American medicine has lost one of its links with the past.

## DR. BENJAMIN JAFFEE BIRK

Benjamin Jaffee Birk, M.D., F.A.C.P., was born in Michigan City, Ind., on August 17, 1894. He received his B.S. degree from the University of Indiana in 1916 and his M.D. degree from Rush Medical College in 1919. He then served internships in the Michael Reese and Cook County Hospitals, Chicago. He did postgraduate work at the University of Chicago School of Medicine, and furthered his studies in internal medicine at the University of Vienna in 1927-28.

As a Milwaukee physician for almost thirty years, Dr. Birk served as Chief Resident, Chief of Staff, Head of Division of Medicine, and finally Head of the Department of Internal Medicine of Mt. Sinai Hospital. From 1940 to 1942 he was an Instructor of Internal Medicine in the Marquette University School of Medicine.

During World War I Dr. Birk served in the Army Medical Corps. He was commissioned in the Army of the United States again in 1942 as a lieutenant-colonel. Before going overseas he was chief of medicine at Fort Sheridan, Ill., after which he was attached to the Chinese Combat Command of the United States Army for thirteen months. In 1944, he was awarded the Legion of Merit with oak leaf cluster for especially meritorious conduct. He was discharged in 1946 with rank of colonel.

Dr. Birk was a member of the Military Order of World Wars, Association of Military Surgeons of the United States, Wisconsin Military Association, Reserve Officers Association, American Medical Association, Wisconsin Heart Association, American Heart Association, Milwaukee Academy of Medicine, Milwaukee County and Wisconsin Medical Societies. He had been a Fellow of the American College of Physicians since 1939.

KARVER L. PUESTOW, M.D., F.A.C.P.,  
Governor for Wisconsin

#### DR. PAUL JAMES CONNOR

With the death of Dr. Paul James Connor of Denver, Colorado has lost one of its most active and capable internists. Dr. Connor was born in Madisonville, Texas, in 1887. He attended the Agricultural and Mechanical College of Texas before entering the University of Texas School of Medicine, from which he graduated in 1912. He came to Colorado from the Ancon Hospital, Canal Zone, in 1920. He was active on the staffs of the Presbyterian, St. Luke's and Mercy Hospitals, of Denver.

A diplomate of the American Board of Internal Medicine, Dr. Connor was particularly interested in endocrinology. He was also very active in the public health work of Colorado, and was President of the State Board of Health in 1931.

He was a member of the Denver City and County and Colorado State Medical Societies, the Inter-State Post Graduate Medical Association of North America, the American Association for the Study of Goiter, the American Diabetes Association, the Association for the Study of Internal Secretions and was a Fellow of the American Medical Association. Dr. Connor had been a Fellow of the American College of Physicians since 1931.

WARD DARLEY, JR., M.D., F.A.C.P.,  
Governor for Colorado

#### DR. HENRY CLAY LONG

Dr. Henry Clay Long, one of Tennessee's well-known medical consultants, died at his home in Knoxville, September 14, 1947.

Dr. Long was born in Marion County, Tenn., October 15, 1878. He attended Pryor Institute and then received his M.D. from Vanderbilt in 1914. His ability as a student is amply shown by his election as a member of the honorary medical society, Alpha Omega Alpha.

His postgraduate study was at the Riverside and Bellevue Hospitals, New York, N. Y., and the New York Post-Graduate Medical School and Hospital. He was a diplomate of the American Board of Internal Medicine.

Dr. Long served in the Army in World War I.

He was a past president of the Knoxville Academy of Medicine, and a Member of the East Tennessee Medical Society, the Tennessee State Medical Society, and the Southern Medical Association. Dr. Long had been a Fellow of the American College of Physicians since 1936.

Dr. Long was a hard worker, a thorough student, and a conscientious physician.

WILLIAM C. CHANEY, M.D., F.A.C.P.,  
Governor for Tennessee

### DR. SAMUEL EDGAR MUNSON

Samuel E. Munson, M.D., F.A.C.P., dean of the medical profession of Springfield, Ill., died on October 2, 1947, at the Memorial Hospital there at the age of 81, following long illness. He is survived by his wife and by his daughter, Miss Mary Munson.

Born in 1866 on a farm in Mechanisburg Township, Sangamon County, Ill., Samuel E. Munson was the son of Joel M. and Elizabeth Van Hook Munson, who had come to the state from Kentucky in 1857. Following three years of study at Valparaiso (Ind.) University, he taught school for three years and began meanwhile the study of medicine with the late Dr. George M. Kreider. He subsequently entered the Northwestern University Medical School and received the M.D. degree in 1893. After several years of practice in Mount Pulaski, he married Miss Daisy North of Rochester, Ill., and went with her to Europe where he attended various clinics in Vienna and studied at the University of Göttingen where, incidentally, his daughter was born. Upon returning to this country, he entered upon his practice of medicine in Springfield, Ill., which continued until a few months before his death. He was a member of the staff of the Springfield Hospital since 1900, and was president of the staff in 1910. From 1936 to 1941 he served as a member of the Medical Advisory Board of the Department of Health of the State of Illinois. In June of 1943, a dinner was held at Springfield in his honor, to mark his completion of fifty years in the practice of medicine, a distinction to which only 290 of the 12,500 physicians in Illinois had then attained. Dr. Munson was a diplomate of the American Board of Internal Medicine.

Dr. Munson received numerous recognitions for his professional work. He was a member and past president of the Illinois State, Central District, and Sangamon County Medical Societies; a member of the Mississippi Valley Medical Society; a Fellow of the American Medical Association. He was also a prominent member of the community as a member of the First Christian Church, as a 32nd degree Mason, past Commander of the Knights Templar; and as member of the Kiwanis Club.

Dr. Munson became a Fellow of the American College of Physicians in 1922. He rendered distinguished service to the College as Governor for Southern Illinois from 1923 to 1941. He was elected Third Vice President of the College for the year 1941-42.

Dr. Munson was held in great esteem by the members of his profession and all who knew him or of him. A skilled physician, he was very highly regarded for his sincerity and modesty and his deep interest in the young physician who sought his advice when getting started in the practice of medicine. His high ethical standards of life and in the practice of medicine deepen the loss of his passing to his family and community.

CECIL M. JACK, M.D., F.A.C.P.,  
Governor for Southern Illinois



## DR. OLIVER WILLIAM WELCH

Oliver William Welch, A.B., M.D., M.P.H., F.A.C.P., Fairfield, Ala., died suddenly in Birmingham, Ala., on October 21, 1947, at the age of 40.

Dr. Welch was born September, 19, 1907, at Talladega, Alabama. He received his pre-medical education at the University of Alabama, and graduated from the Harvard Medical School in 1933. He did postgraduate work at the Boston City Hospital, Massachusetts General Hospital, and the Harvard School of Public Health, where he received his Master's Degree in Public Health in June, 1936. He then served as Associate Medical Officer in charge of Industrial Hygiene for the Tennessee Valley Authority until August, 1938, when he became permanently associated with the Department of Medicine of the Employees' Hospital, Tennessee Coal, Iron and Railroad Company, Fairfield, Ala. He was Chief of the Medical Service of this hospital at the time of his death. He had served overseas for two years during World War II.

Dr. Welch was a member of the Jefferson County Medical Association and of the Medical Association of the State of Alabama, and a Fellow of the American Medical Association. A diplomate of the American Board of Internal Medicine, he was elected to Fellowship in the American College of Physicians in April, 1947.

Dr. Welch was a keen clinician. He will be missed by his associates and his community.

E. DICE LINEBERRY, M.D., F.A.C.P.,  
Governor for Alabama

